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(54) Title: INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME			
(57) Abstract			
<p>The present invention relates to novel classes of compounds which are inhibitors of interleukin-1β converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against IL-1-, apoptosis-, IGIF-, and IFN-γ-mediated diseases, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, and necrotic diseases. This invention also relates to methods for inhibiting ICE activity, for treating interleukin-1-, apoptosis-, IGIF- and IFN-γ-mediated diseases and decreasing IGIF and IFN-γ production using the compounds and compositions of this invention. This invention also relates to methods for preparing N-acylamino compounds.</p>			

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INHIBITORS OF INTERLEUKIN-1 β CONVERTING ENZYMETECHNICAL FIELD OF THE INVENTION

The present invention relates to novel
5 classes of compounds which are inhibitors of
interleukin-1 β converting enzyme ("ICE"). This
invention also relates to pharmaceutical compositions
comprising these compounds. The compounds and
pharmaceutical compositions of this invention are
10 particularly well suited for inhibiting ICE activity
and consequently, may be advantageously used as agents
against interleukin-1- ("IL-1"), apoptosis-, interferon
gamma inducing factor- ("IGIF") and interferon- γ -
("IFN- γ ") mediated diseases, including inflammatory
15 diseases, autoimmune diseases, destructive bone,
proliferative disorders, infectious diseases and
degenerative diseases. This invention also relates to
methods for inhibiting ICE activity, and decreasing
IGIF production and IFN- γ production and methods for
20 treating interleukin-1-, apoptosis-, IGIF- and IFN- γ -
mediated diseases using the compounds and compositions
of this invention. This invention also relates to
methods of preparing N-acylamino compounds.

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BACKGROUND OF THE INVENTION

Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins, collagenase and phospholipase by synovial cells and chondrocytes, basophil and eosinophil degranulation and neutrophil activation. Oppenheim, J.H. et al., Immunology Today, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. For example, in rheumatoid arthritis, IL-1 is both a mediator of inflammatory symptoms and of the destruction of the cartilage proteoglycan in afflicted joints. Wood, D.D. et al., Arthritis Rheum. 26, 975, (1983); Pettipher, E.J. et al., Proc. Natl. Acad. Sci. UNITED STATES OF AMERICA 71, 295 (1986); Arend, W.P. and Dayer, J.M., Arthritis Rheum. 38, 151 (1995). IL-1 is also a highly potent bone resorption agent. Jandiski, J.J., J. Oral Path 17, 145 (1988); Dewhirst, F.E. et al., J. Immunol. 8, 2562 (1985). It is alternately referred to as "osteoclast activating factor" in destructive bone diseases such as osteoarthritis and multiple myeloma. Bataille, R. et al., Int. J. Clin. Lab. Res. 21(4), 283 (1992). In certain proliferative disorders, such as acute myelogenous leukemia and multiple myeloma, IL-1 can promote tumor cell growth and adhesion. Bani, M.R., J. Natl. Cancer Inst. 83, 123 (1991); Vidal-Vanaclocha, F., Cancer Res. 54, 2667 (1994). In these disorders, IL-1 also stimulates production of other cytokines such as IL-6, which can modulate tumor development (Tartour et al., Cancer Res. 54, 6243 (1994)). IL-1 is predominantly produced by peripheral blood monocytes as part of the inflammatory response

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and exists in two distinct agonist forms, IL-1 α and IL-1 β . Mosely, B.S. et al., Proc. Natl. Acad. Sci., 84, pp. 4572-4576 (1987); Lonnemann, G. et al., Eur. J. Immunol., 19, pp. 1531-1536 (1989).

5 IL-1 β is synthesized as a biologically inactive precursor, pIL-1 β . pIL-1 β lacks a conventional leader sequence and is not processed by a signal peptidase. March, C.J., Nature, 315, pp. 641-647 (1985). Instead, pIL-1 β is cleaved by 10 interleukin-1 β converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R., et al., J. Biol. Chem., 265, pp. 14526-14528 (1992); A.D. Howard et al., J. Immunol., 147, pp. 2964-2969 (1991). ICE is a cysteine protease localized primarily in monocytes. It converts 15 precursor IL-1 β to the mature form. Black, R.A. et al., FEBS Lett., 247, pp. 386-390 (1989); Kostura, M.J. et al., Proc. Natl. Acad. Sci. UNITED STATES OF AMERICA, 86, pp. 5227-5231 (1989). Processing by ICE 20 is also necessary for the transport of mature IL-1 β through the cell membrane.

ICE, or its homologs, also appears to be involved in the regulation of programmed cell death or 25 apoptosis. Yuan, J. et al., Cell, 75, pp. 641-652 (1993); Miura, M. et al., Cell, 75, pp. 653-660 (1993); Nett-Fiordalisi, M.A. et al., J. Cell Biochem., 17B, p. 117 (1993). In particular, ICE or ICE homologs are thought to be associated with the regulation of 30 apoptosis in neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259, pp. 760-762 (1993); Gagliardini, V. et al., Science, 263, pp. 826-828 (1994). Therapeutic applications for inhibition of apoptosis

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may include treatment of Alzheimer's disease, Parkinson's disease, stroke, myocardial infarction, spinal atrophy, and aging.

ICE has been demonstrated to mediate apoptosis (programmed cell death) in certain tissue types. Steller, H., Science, 267, p. 1445 (1995); Whyte, M. and Evan, G., Nature, 376, p. 17 (1995); Martin, S.J. and Green, D.R., Cell, 82, p. 349 (1995); Alnemri, E.S., et al., J. Biol. Chem., 270, p. 4312 (1995); Yuan, J. Curr. Opin. Cell Biol., 7, p. 211 (1995). A transgenic mouse with a disruption of the ICE gene is deficient in Fas-mediated apoptosis (Kuida, K. et al., Science 267, 2000 (1995)). This activity of ICE is distinct from its role as the processing enzyme for pro-IL1 β . It is conceivable that in certain tissue types, inhibition of ICE may not affect secretion of mature IL-1 β , but may inhibit apoptosis.

Enzymatically active ICE has been previously described as a heterodimer composed of two subunits, p20 and p10 (20kDa and 10kDa molecular weight, respectively). These subunits are derived from a 45kDa proenzyme (p45) by way of a p30 form, through an activation mechanism that is autocatalytic.

Thornberry, N.A. et al., Nature, 356, pp. 768-774 (1992). The ICE proenzyme has been divided into several functional domains: a prodomain (p14), a p22/20 subunit, a polypeptide linker and a p10 subunit. Thornberry et al., supra; Casano et al., Genomics, 20, pp. 474-481 (1994).

Full length p45 has been characterized by its cDNA and amino acid sequences. PCT patent applications WO 91/15577 and WO 94/00154. The p20 and p10 cDNA and amino acid sequences are also known. Thornberry et al., supra. Murine and rat ICE have also been sequenced and cloned. They have high amino acid and

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nucleic acid sequence homology to human ICE. Miller, D.K. et al., Ann. N.Y. Acad. Sci., 696, pp. 133-148 (1993); Molineaux, S.M. et al., Proc. Nat. Acad. Sci., 90, pp. 1809-1813 (1993). The three-dimensional structure of ICE has been determined at atomic resolution by X-ray crystallography. Wilson, K.P., et al., Nature, 370, pp. 270-275 (1994). The active enzyme exists as a tetramer of two p20 and two p10 subunits.

10 Additionally, there exist human homologs of ICE with sequence similarities in the active site regions of the enzymes. Such homologs include TX (or ICE_{rel-II} or ICH-2) (Faucheu, et al., EMBO J., 14, p. 1914 (1995); Kamens J., et al., J. Biol. Chem., 270, p. 15250 (1995); Nicholson et al., J. Biol. Chem., 270 15 15870 (1995)), TY (or ICE_{rel-III}) (Nicholson et al., J. Biol. Chem., 270, p. 15870 (1995); ICH-1 (or Nedd-2) (Wang, L. et al., Cell, 78, p. 739 (1994)), MCH-2, (Fernandes-Alnemri, T. et al., Cancer Res., 55, p. 2737 20 20 (1995)), CPP32 (or YAMA or apopain) (Fernandes-Alnemri, T. et al., J. Biol. Chem., 269, p. 30761 (1994)); Nicholson, D.W. et al., Nature, 376, p. 37 (1995)), and CMH-1 (or MCH-3) (Lippke, et al., J. Biol. Chem., 1996); Fernandes-Alnemri, T. et al., Cancer Res., 25 25 (1995)). Each of these ICE homologs, as well as ICE itself, is capable of inducing apoptosis when overexpressed in transfected cell lines. Inhibition of one or more of these homologs with the peptidyl ICE inhibitor Tyr-Val-Ala-Asp-chloromethylketone results in inhibition of apoptosis in primary cells or cell lines. Lazebnik et al., Nature, 371, p. 346 (1994). The compounds described herein are also capable of inhibiting one or more homologs of ICE (see Example 5). Therefore, these compounds may be used to inhibit 30 30 apoptosis in tissue types that contain ICE homologs, but which do not contain active ICE or produce mature 35 35

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IL-1 β .

Interferon-gamma inducing factor (IGIF) is an approximately 18-kDa polypeptide that stimulates T-cell production of interferon-gamma (IFN- γ). IGIF is produced by activated Kupffer cells and macrophages in vivo and is exported out of such cells upon endotoxin stimulation. Thus, a compound that decreases IGIF production would be useful as an inhibitor of such T-cell stimulation which in turn would reduce the levels of IFN- γ production by those cells.

IFN- γ is a cytokine with immunomodulatory effects on a variety of immune cells. In particular, IFN- γ is involved in macrophage activation and Th1 cell selection (F. Belardelli, APMIS, 103, p. 161 (1995)). IFN- γ exerts its effects in part by modulating the expression of genes through the STAT and IRF pathways (C. Schindler and J.E. Darnell, Ann. Rev. Biochem., 64, p. 621 (1995); T. Taniguchi, J. Cancer Res. Clin. Oncol., 121, p. 516 (1995)).

Mice lacking IFN- γ or its receptor have multiple defects in immune cell function and are resistant to endotoxic shock (S. Huang et al., Science, 259, p. 1742 (1993); D. Dalton et al., Science, 259, p. 1739 (1993); B. D. Car et al., J. Exp. Med., 179, p. 1437 (1994)). Along with IL-12, IGIF appears to be a potent inducer of IFN- γ production by T cells (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995); S. Ushio et al., J. Immunol., 156, p. 4274 (1996)).

IFN- γ has been shown to contribute to the pathology associated with a variety of inflammatory, infectious and autoimmune disorders and diseases. Thus, compounds capable of decreasing IFN- γ production

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would be useful to ameliorate the effects of IFN- γ related pathologies.

The biological regulation of IGIF and thus IFN- γ has not been elucidated. It is known that IGIF is synthesized as a precursor protein, called "pro-IGIF". It has been unclear, however, how pro-IGIF is cleaved and whether its processing has biological importance.

Accordingly, compositions and methods capable of regulating the conversion of pro-IGIF to IGIF would be useful for decreasing IGIF and IFN- γ production in vivo, and thus for ameliorating the detrimental effects of these proteins which contribute to human disorders and diseases.

However, ICE and other members of the ICE/CED-3 family have not previously been linked to the conversion of pro-IGIF to IGIF or to IFN- γ production in vivo.

ICE inhibitors represent a class of compounds useful for the control of inflammation or apoptosis or both. Peptide and peptidyl inhibitors of ICE have been described. PCT patent applications WO 91/15577; WO 93/05071; WO 93/09135; WO 93/14777 and WO 93/16710; and European patent application 0 547 699. Such peptidyl inhibitors of ICE has been observed to block the production of mature IL-1 β in a mouse model of inflammation (*vide infra*) and to suppress growth of leukemia cells *in vitro* (Estrov et al., Blood 84, 380a (1994)). However, due to their peptidic nature, such inhibitors are typically characterized by undesirable pharmacologic properties, such as poor cellular penetration and cellular activity, poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in Drug Discovery

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Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126. This has hampered their development into effective drugs.

Non-peptidyl compounds have also been
5 reported to inhibit ICE in vitro. PCT patent application WO 95/26958; US Patents 5,552,400; Dolle et al., J. Med. Chem., 39, pp. 2438-2440 (1996); However, it is not clear whether these compounds have the appropriate pharmacological profile to be
10 therapeutically useful.

Additionally, current methods for the preparation of such compounds are not advantageous. These methods use tributyltin hydride, a toxic, moisture sensitive reagent. Thus, these methods are
15 inconvenient to carry out, pose a health risk and create toxic-waste disposal problems. Furthermore, it is difficult to purify compounds prepared by these methods.

Accordingly, the need exists for compounds
20 that can effectively inhibit the action of ICE in vivo, for use as agents for preventing and treating chronic and acute forms of IL-1-mediated diseases, apoptosis-, IGF-, or IFN- γ -mediated diseases, as well as inflammatory, autoimmune, destructive bone, proliferative, infectious, or degenerative diseases.
25 The need also exists for methods of preparing such compounds.

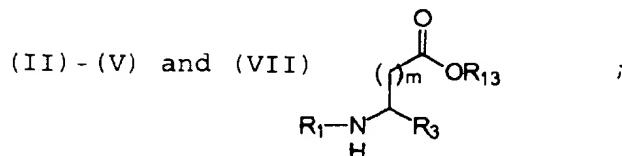
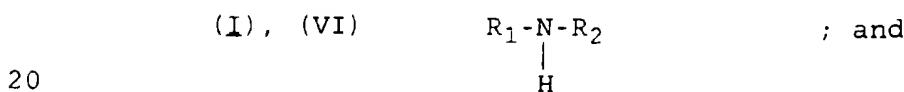
SUMMARY OF THE INVENTION

The present invention provides novel classes
30 of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of ICE. These compounds can be used alone or in combination with other therapeutic or prophylactic agents, such as antibiotics, immunomodulators or other anti-inflammatory agents, for the treatment or
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prophylaxis of diseases mediated by IL-1, apoptosis, 5 IGIF or IFN- γ . According to a preferred embodiment, the compounds of this invention are capable of binding to the active site of ICE and inhibiting the activity of that enzyme. Additionally, they have improved cellular potency, improved pharmacokinetics, and/or improved oral bioavailability compared to peptidyl ICE inhibitors.

10 It is a principal object of this invention to provide novel classes of compounds which are inhibitors of ICE represented by formulas:



wherein the various substituents are described herein.

25 It is a further object of this invention to provide a process of preparing N-acylamino compounds by coupling a carboxylic acid with an alloc-protected amine.

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BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A ICE cleaves pro-IGIF in vivo. Cell lysates from Cos cells transfected with the various indicated expression plasmids or controls were analyzed for the presence of IGIF by separating proteins by SDS-PAGE and immunoblotting with anti-IGIF antisera (lane 1, mock transfected cells; lane 2, pro-IGIF alone; lanes 3-12, pro-IGIF in combination with ICE, ICE-C285S, CPP32, CPP32-C163S, CMH-1, CMH-1-C186S, Tx, Tx-C258S, respectively). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular weight markers in kDa are shown on the left (Example 23).

Fig. 1B ICE cleaves pro-IGIF at the authentic processing site in vitro as shown by Coomassie blue staining of proteolytic reaction products separated by SDS-PAGE (Example 23). The proteases and inhibitors used were: lane 1, buffer control; lane 2, 0.1 nM ICE; lane 3, 1 nM ICE; lanes 4 and 5, 1 nM ICE with 10 nM Cbz-Val-Ala-Asp-[(2,6-dichlorobenzoyl)oxy]methyl ketone and 100 nM Ac-Tyr-Val-Ala-Asp-aldehyde, respectively; lanes 6 and 7, 15 nM CPP32 with and without 400 nM Ac-Asp-Glu-Val-Asp-aldehyde (D. W. Nicholson et al., Nature, 376, p. 37 (1995)), respectively; lane 8, 100 nM CMH-1; lane 9, 10 units/ml granzyme B; and M, molecular weight markers in kDa.

Fig. 1C ICE cleavage converts inactive pro-IGIF to active IGIF which induces IFN- γ production in Th1 helper cells. Uncleaved (Pro-IGIF), ICE-cleaved (Pro-IGIF/ICE), CPP32-cleaved (Pro-IGIF/CPP32), and recombinant mature IGIF (rIGIF) were incubated with

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A.E7 Th1 cells at 12 ng/ml (open bar) and 120 ng/ml (hatched bar) for eighteen hours and the levels of IFN- γ released into the culture medium assayed by ELISA (Example 23). A.E7 cells cultured with buffer, ICE alone (ICE) or CPP32 alone (CPP32) were assayed similarly for negative controls. The numbers represent the average of three determinations.

Fig. 2A Mature IGIF (18-kDa) is produced by Cos cells co-transfected with pro-IGIF and ICE-expressing plasmids. Cell lysates (left) and conditioned medium (right) from Cos cells transfected with a pro-IGIF expression plasmid in the absence (-) or presence of an expression plasmid encoding wild type (ICE) or inactive mutant (ICE-C285S) ICE. Transfected cells were metabolically labeled with 35 S-methionine, proteins from cell lysates and conditioned medium immunoprecipitated with anti-IGIF antisera and separated by SDS-PAGE (Example 24). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular weight markers in kDa are shown on the left.

Fig. 2B IFN- γ inducing activity is detected in Cos cells co-transfected with pro-IGIF and ICE-expressing plasmids. Cell lysates (hatched bar) and conditioned medium (open bar) from Cos cells transfected with a pro-IGIF expression plasmid in the absence (Pro-IGIF) or presence (Pro-IGIF/ICE) of an expression plasmid encoding wild type (ICE) were assayed for IFN- γ levels (ng/ml) by ELISA. Cos cells transfected with buffer (Mock) or an ICE-expressing plasmid alone (ICE) served as negative controls (Example 24).

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5 **Fig. 3A** Kupffer cells from mice lacking ICE are defective in the export of IGIF. Kupffer cells from wild type mice (ICE +/+) or ICE-deficient mice homozygous for an ICE mutation (ICE -/-) were isolated and primed with LPS for three hours. The levels of immunoreactive IGIF polypeptides in the conditioned media (ng/ml) of wild type cells were measured by ELISA (Example 25). N.D. (not detectable) indicates that the IGIF concentration was less than 0.1 ng/ml.

10 **Fig. 3B** Kupffer cells from mice lacking ICE are defective in the export of mature IGIF. Kupffer cells from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were isolated and primed with LPS for three hours. Primed cells were metabolically labeled with ³⁵S-methionine, proteins from cell lysates and conditioned medium immunoprecipitated with anti-IGIF antisera and separated by SDS-PAGE (Example 25). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular mass markers in kDa are shown on the left.

25 **Fig. 3C** Serum from ICE-deficient mice contains reduced levels of IGIF. Serum samples from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were assayed for IGIF levels (ng/ml) by ELISA (Example 25).

30 **Fig. 3D** Serum from ICE-deficient mice contains reduced levels of IFN- γ . Serum samples from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were assayed for IFN- γ levels (ng/ml) by ELISA (Example 25).

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5 **Fig. 4** Serum IFN- γ levels are significantly reduced in ICE-deficient mice after an acute challenge with LPS (Example 26). Serum samples from wild type mice (filled squares) or ICE-deficient mice (filled circles) were assayed for IFN- γ levels (ng/ml) by ELISA as a function of time (hours) after LPS challenge. Temperatures of the animals during the time course in degrees Celcius is shown for wild type mice (open squares) or ICE-deficient mice (open circles).

10 **Fig. 5** The ICE inhibitor, AcYVAD-aldehyde (AcYVAD-CHO), inhibits LPS-stimulated IL-1 β and IFN- γ synthesis by human peripheral blood mononuclear cells (PBMC). Percent (%) inhibition as a function of inhibitor concentration (μ M) is shown for IL-1 β (open squares) and IFN- γ (open diamonds) synthesis.

20 **Fig. 6** Compound 214e inhibits IL-1 β production in LPS-challenged mice. Serum samples from CD1 mice were assayed for IL-1 β levels (pg/ml) by ELISA after LPS challenge. Compound 214e was administered by intraperitoneal (IP) injection one hour after LPS challenge. Blood was collected seven hours after LPS challenge (see Example 7).

25 **Fig. 7** Compound 217e inhibits IL-1 β production in LPS-challenged mice. Serum samples from CD1 mice were assayed for IL-1 β levels (pg/ml) by ELISA after LPS challenge. Compound 217e was administered by intraperitoneal (IP) injection one hour after LPS challenge. Blood was collected seven hours after LPS challenge (see Example 7).

30 **Fig. 8** Compound 214e, but not compound 217e,

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inhibits IL-1 β production in LPS-challenged mice when administered by oral gavage. This assay measures oral absorption under similar conditions as those described for Figs. 6 and 7. These results indicates that 214e
5 is potentially orally active as an ICE inhibitor (see Example 7).

Fig. 9 Compound 214e and analogs of 214e also inhibit IL-1 β production after IP administration. These results were obtained in the assay described for
10 Figs. 6 and 7 and Example 7.

Fig. 10 Compound 214e, and analogs of 214e, also inhibit IL-1 β production after oral (PO) administration. These results were obtained in the assay described for Figs. 6 and 7 and Example 7.

15 Figs. 11A/B Compounds 302 and 304a show detectable blood levels when administered orally (50mg/kg, in 0.5 % carboxymethylcellulose) to mice. Blood samples were collected at 1 and 7 hours after dosing. Compounds 302 and 304a are prodrugs of 214e and are metabolized to
20 214e *in vivo*. Compound 214e shows no blood levels above 0.10 μ g/ml when administered orally (Example 8).

Fig. 12 Compound 412f blocks the progression of type II collagen-induced arthritis in male DBA/1J mice (Wooley, P.H., Methods in Enzymology, 162, pp. 361-373
25 (1988) and Geiger, T., Clinical and Experimental Rheumatology, 11, pp. 515-522 (1993)). Compound 412f was administered twice a day (10, 25 and 50mg/kg), approximately 7h apart, by oral gavage. Inflammation was measured on the Arthritis Severity Score on a 1 to
30 4 scale of increasing severity. The scores of the two front paws were added to give the final score (see Example 21).

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Fig. 13 Compound 412d blocks the progression of type II collagen-induced arthritis in male DBA/1J mice. The results were obtained as described for Fig. 12 and in Example 21.

5 **Fig. 14** Compound 696a blocks the progression of type II collagen-induced arthritis in male DBA/1J mice. The results were obtained as described for Fig. 12 and in Example 21.

ABBREVIATIONS AND DEFINITIONS

		<u>Abbreviations</u>
	<u>Designation</u>	<u>Reagent or Fragment</u>
10	Ala	alanine
	Arg	arginine
	Asn	asparagine
15	Asp	aspartic acid
	Cys	cysteine
	Gln	glutamine
	Glu	glutamic acid
	Gly	glycine
20	His	histidine
	Ile	isoleucine
	Leu	leucine
	Lys	lysine
	Met	methionine
25	Phe	phenylalanine
	Pro	proline
	Ser	serine
	Thr	threonine
	Trp	tryptophan
30	Tyr	tyrosine
	Val	valine
	Ac ₂ O	acetic anhydride
	n-Bu	normal-butyl

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	DMF	dimethylformamide
	DIEA	<i>N,N</i> -diisopropylethylamine
	EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
5	Et ₂ O	diethyl ether
	EtOAc	ethyl acetate
	Fmoc	9-fluorenylmethyloxycarbonyl
	HBTU	O-benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium
10		hexafluorophosphate
	HOBT	1-hydroxybenzotriazole hydrate
	MeOH	methanol
	TFA	trifluoroacetic acid
	Alloc	allyloxycarbonyl

15

Definitions

The following terms are employed herein:

The term "interferon gamma inducing factor" or "IGIF" refers to a factor which is capable of 20 stimulating the endogenous production of IFN-γ.

The term "ICE inhibitor" refers to a compound which is capable of inhibiting the ICE enzyme. ICE inhibition may be determined using the methods described and incorporated by reference herein. The 25 skilled practitioner realizes that an in vivo ICE inhibitor is not necessarily an in vitro ICE inhibitor. For example, a prodrug form of a compound typically demonstrates little or no activity in in vitro assays. Such prodrug forms may be altered by metabolic or other 30 biochemical processes in the patient to provide an in vivo ICE inhibitor.

The term "cytokine" refers to a molecule which mediates interactions between cells.

The term "condition" refers to any disease,

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disorder or effect that produces deleterious biological consequences in a subject.

The term "subject" refers to an animal, or to one or more cells derived from an animal. Preferably, the animal is a mammal, most preferably a human. Cells may be in any form, including but not limited to cells retained in tissue, cell clusters, immortalized cells, transfected or transformed cells, and cells derived from an animal that have been physically or phenotypically altered.

The term "active site" refers to any or all of the following sites in ICE: the substrate binding site, the site where an inhibitor binds and the site where the cleavage of substrate occurs.

The term "heterocycle" or "heterocyclic" refers to a stable mono- or polycyclic compound which may optionally contain one or two double bonds or may optionally contain one or more aromatic rings. Each heterocycle consists of carbon atoms and from one to four heteroatoms independently selected from a group including nitrogen, oxygen, and sulfur. As used herein, the terms "nitrogen heteroatoms" and "sulphur heteroatoms" include any oxidized form of nitrogen or sulfur and the quaternized form of any basic nitrogen. Heterocycles defined above include, for example, pyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinonlinyl, purinyl, pyrimidyl, indolinyl, benzimidazolyl, imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, β -carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl, oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl,

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tetrahydropyranyl, tetrahydrofuryl, thiadiazolyl, benzodioxolyl, benzothienyl, tetrahydrothiophenyl and sulfolanyl. Further heterocycles are described in A.R. Katritzky and C.W. Rees, eds., Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Use of Heterocyclic Compounds, Vol. 1-8, Pergamon Press, NY (1984).

The term "cycloalkyl" refers to a mono- or polycyclic group which contains 3 to 15 carbons and may 10 optionally contain one or two double bonds. Examples include cyclohexyl, adamantyl and norbornyl.

The term "aryl" refers to a mono- or polycyclic group which contains 6, 10, 12, or 14 15 carbons in which at least one ring is aromatic.

Examples include phenyl, naphthyl, and tetrahydronaphthalene.

The term "heteroaromatic" refers to a mono- or polycyclic group which contains 1 to 15 carbon atoms and from 1 to 4 heteroatoms, each of which is selected 20 independently from a group including sulphur, nitrogen and oxygen, and which additionally contains from 1 to 3 five or six membered rings, at least one of which is aromatic.

The term "alpha-amino acid" (α -amino acid) 25 refers to both the naturally occurring amino acids and other "non-protein" α -amino acids commonly utilized by those in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The naturally occurring amino acids are glycine, alanine, valine, leucine, iso-leucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ -carboxyglutamic acid, arginine, ornithine and lysine. 30 Examples of "non-protein" alpha-amino acids include 35

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hydroxylysine, homoserine, homotyrosine, homo-
phenylalanine, citrulline, kynurenone, 4-amino-
phenylalanine, 3-(2-naphthyl)-alanine, 3-(1-naphthyl)-
alanine, methionine sulfone, t-butyl-alanine,
5 t-butylglycine, 4-hydroxyphenylglycine, aminoalanine,
phenylglycine, vinylalanine, propargyl-glycine,
1,2,4-triazolo-3-alanine, 4,4,4-trifluoro-threonine,
thyonine, 6-hydroxytryptophan, 5-hydroxytryptophan,
3-hydroxykynurenone, 3-aminotyrosine, trifluoromethyl-
alanine, 2-thienylalanine, (2-(4-pyridyl)ethyl)-
10 cysteine, 3,4-dimethoxy-phenylalanine, 3-(2-thiazolyl)-
alanine, ibotenic acid, 1-amino-1-cyclopentane-
carboxylic acid, 1-amino-1-cyclohexanecarboxylic acid,
quisqualic acid, 3-trifluoromethylphenylalanine,
15 4-trifluoro-methylphenylalanine, cyclohexylalanine,
cyclo-hexylglycine, thiohistidine, 3-methoxytyrosine,
elastatinal, norleucine, norvaline, alloisoleucine,
homoarginine, thioproline, dehydroproline, hydroxy-
proline, isonipectotic acid, homoproline, cyclohexyl-
20 glycine, α -amino-n-butyric acid, cyclohexylalanine,
aminophenylbutyric acid, phenylalanines substituted at
the ortho, meta, or para position of the phenyl moiety
with one or two of the following: a (C₁-C₄) alkyl, a
(C₁-C₄) alkoxy, halogen or nitro groups or substituted
25 with a methylenedioxy group; β -2- and 3-thienyl-
alanine, β -2- and 3-furanylalanine, β -2-, 3- and
4-pyridylalanine, β -(benzothienyl-2- and 3-yl)alanine,
 β -(1- and 2-naphthyl)alanine, O-alkylated derivatives
of serine, threonine or tyrosine, S-alkylated cysteine,
30 S-alkylated homocysteine, O-sulfate, O-phosphate and O-
carboxylate esters of tyrosine, 3-sulfo-tyrosine, 3-
carboxy-tyrosine, 3-phospho-tyrosine, 4-methane
sulfonic acid ester of tyrosine, 4-methane phosphonic
acid ester of tyrosine, 3,5-diiodotyrosine, 3-nitro-
35 tyrosine, ϵ -alkyl lysine, and delta-alkyl ornithine.

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Any of these α -amino acids may be substituted with a methyl group at the alpha position, a halogen at any aromatic residue on the α -amino side chain, or an appropriate protective group at the O, N, or S atoms of the side chain residues. Appropriate protective groups are disclosed in "Protective Groups In Organic Synthesis," T.W. Greene and P.G.M. Wuts, J. Wiley & Sons, NY, NY, 1991.

The term "substitute" refers to the replacement of a hydrogen atom in a compound with a substituent group. In the present invention, those hydrogen atoms which form a part of a hydrogen bonding moiety which is capable of forming a hydrogen bond with the carbonyl oxygen of Arg-341 of ICE or the carbonyl oxygen of Ser-339 of ICE are excluded from substitution. These excluded hydrogen atoms include those which comprise an -NH- group which is alpha to a -CO- group and are depicted as -NH- rather than an X group or some other designation in the following diagrams: (a) through (t), (v) through (z).

The term "straight chain" refers to a contiguous unbranching string of covalently bound atoms. The straight chain may be substituted, but these substituents are not a part of the straight chain.

The term " K_i " refers to a numerical measure of the effectiveness of a compound in inhibiting the activity of a target enzyme such as ICE. Lower values of K_i reflect higher effectiveness. The K_i value is derived by fitting experimentally determined rate data to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The term "patient" as used in this application refers to any mammal, especially humans.

The term "pharmaceutically effective amount" refers to an amount effective in treating or

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ameliorating an IL-1-, apoptosis-, IGIF- or IFN- γ -mediated disease in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially lessening
5 IL-1-, apoptosis-, IGIF or IFN- γ mediated diseases in a patient.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy
10 the pharmacological activity thereof.

15 The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an anti-ICE active metabolite or residue thereof.

Pharmaceutically acceptable salts of the
20 compounds of this invention include, for example, those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic,
25 lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable,
30 may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C₁₋₄ alkyl)₄⁺
35

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salts.

This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic 5 nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diethyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such 10 15 quaternization.

The ICE inhibitors of this invention may contain one or more "asymmetric" carbon atoms and thus may occur as racemates and racemic mixtures, single 20 enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although specific compounds and scaffolds exemplified in this application may be 25 depicted in a particular stereochemical configuration, compounds and scaffolds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

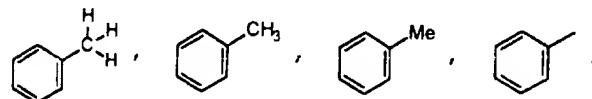
The ICE inhibitors of this invention may 30 comprise ring structures which may optionally be substituted at carbon, nitrogen or other atoms by various substituents. Such ring structures may be singly or multiply substituted. Preferably, the ring structures contain between 0 and 3 substituents. When 35 multiply substituted, each substituent may be picked independently of any other substituent as long as the

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combination of substituents results in the formation of a stable compound.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

Substituents may be represented in various forms. These various forms are known to the skilled practitioner and may be used interchangeably. For example, a methyl substituent on a phenyl ring may be represented in any of the following forms:



Various forms of substituents such as methyl are used herein interchangeably.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth.

The ICE inhibitors of one embodiment (A) of this invention are those of formula α :



wherein:

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X_1 is -CH;

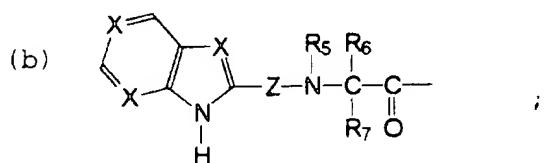
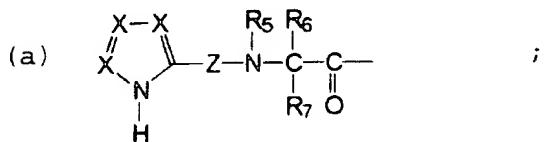
g is 0 or 1;

each J is independently selected from the group
consisting of -H, -OH, and -F, provided that when a
5 first and second J are bound to a C and said first J is
-OH, said second J is -H;

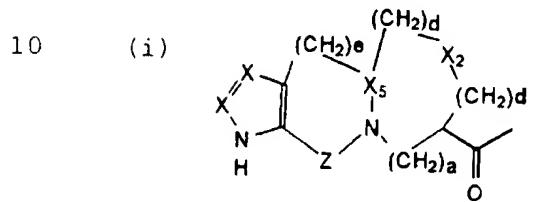
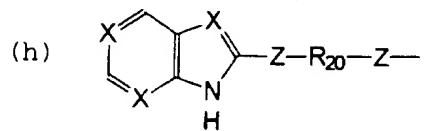
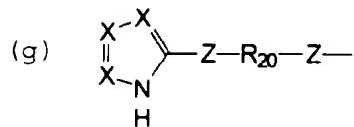
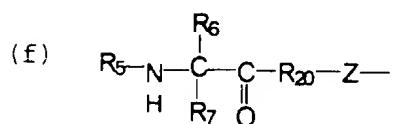
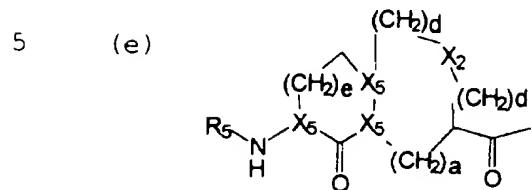
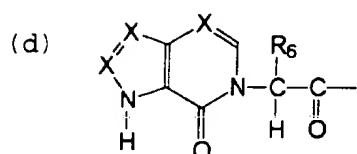
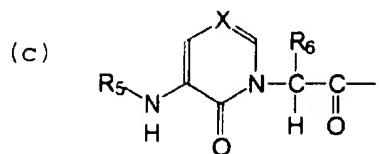
m is 0, 1, or 2;

T is -OH, -CO-CO₂H, -CO₂H, or any bioisosteric
replacement for -CO₂H;

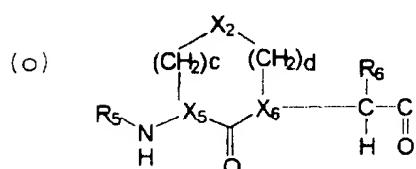
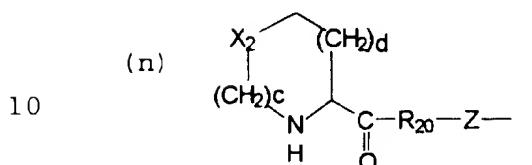
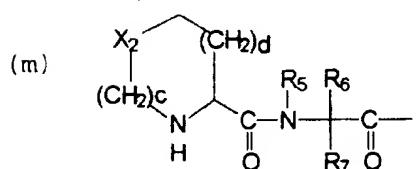
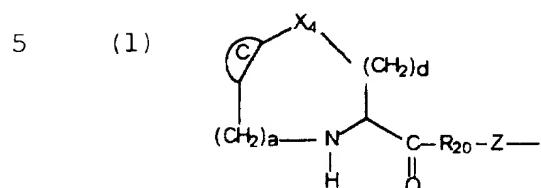
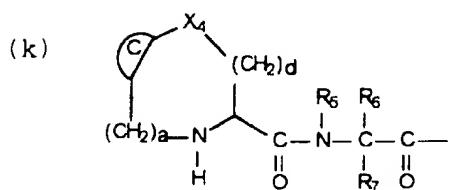
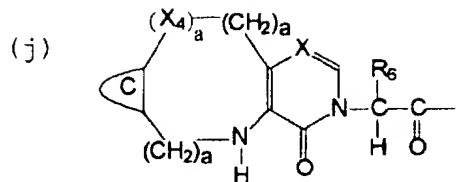
10 R₁ is selected from the group consisting of the
following formulae, in which any ring may optionally be
singly or multiply substituted at any carbon by Q₁, at
any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H,
or halogen; any saturated ring may optionally be
15 unsaturated at one or two bonds; and wherein R₁ (e) and
R₁ (y) are optionally benzofused;



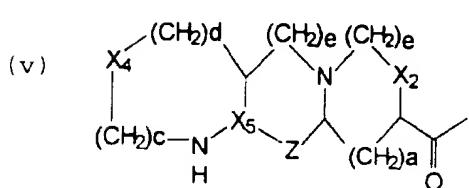
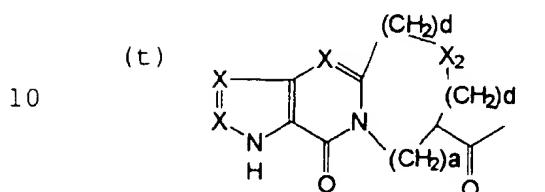
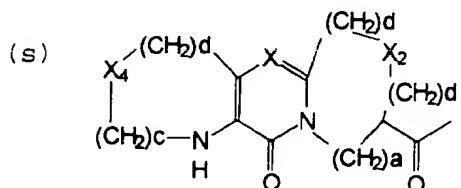
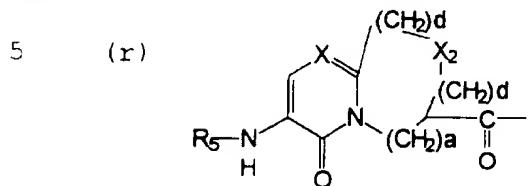
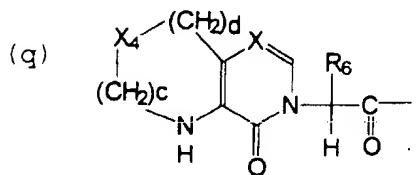
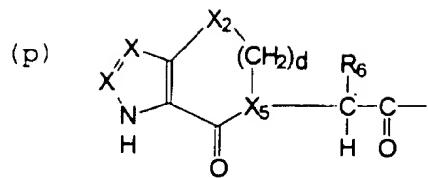
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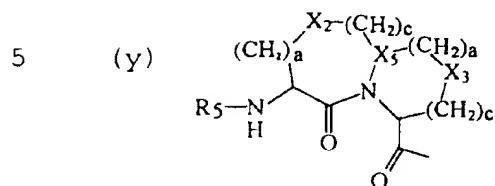
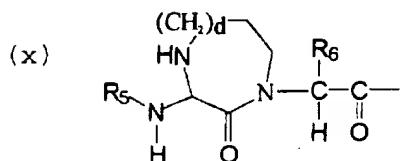
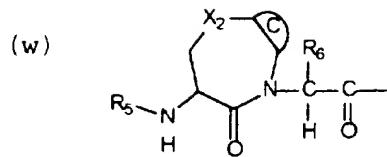
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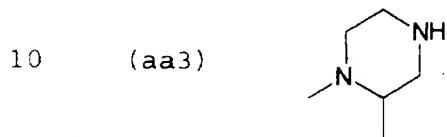
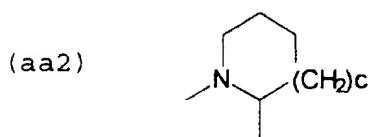
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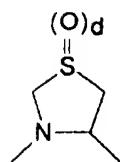


R₂₀ is selected from the group consisting of:



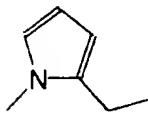
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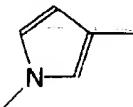
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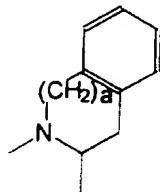
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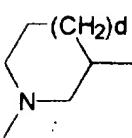
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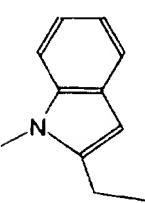
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(ee)



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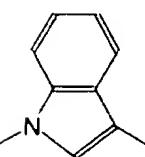
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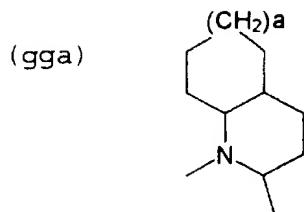
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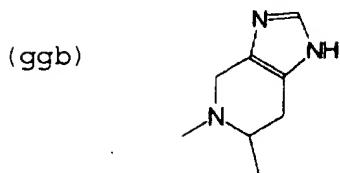


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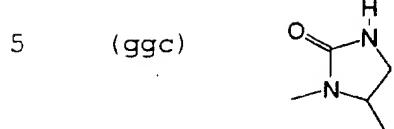
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;



; and



;

wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, 10 pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R₃ is:

- CN,
- CH=CH-R₉,
- CH=N-O-R₉,
- 15 - (CH₂)₁₋₃-T₁-R₉,
- CJ₂-R₉,
- CO-R₁₃, or
- /R₅
- 20 - CO-CO-N \R₁₀;

each R₄ is independently selected from the group consisting of:

- H,
- Ar₁,
- 25 -R₉,
- T₁-R₉, and

- 31 -

- $(\text{CH}_2)_{1,2,3}$ - T_1 - R_9 ;

each T_1 is independently selected from the group consisting of:

- CH=CH-,
- 5 -O-,
- S-,
- SO-,
- SO₂-,
- NR₁₀-,
- 10 -NR₁₀-CO-,
- CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀-,
- 15 -O-CO-NR₁₀-,
- NR₁₀-CO-O-,
- NR₁₀-CO-NR₁₀-,
- SO₂-NR₁₀-,
- NR₁₀-SO₂-, and
- 20 -NR₁₀-SO₂-NR₁₀-;

each R_5 is independently selected from the group consisting of:

- H,
- 25 -Ar₁,
- CO-Ar₁,
- SO₂-Ar₁,
- CO-NH₂,
- SO₂-NH₂,
- R₉,
- 30 -CO-R₉,
- CO-O-R₉,
- SO₂-R₉,

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$$-\text{CO}-\overset{\text{/Ar}_1}{\underset{\text{\textbackslash R}_{10}}{\text{N}}}$$

$$5 \quad -\text{SO}_2-\text{N}^{\text{/Ar}_1}_{\text{\textbackslash R}_{10}},$$

$$-\text{CO}-\overset{\text{R}_9}{\underset{\text{R}_{10}}{\text{N}}}, \quad \text{and}$$

$$10 \quad \begin{array}{c} /R_9 \\ -SO_2-N \\ \backslash R_{10}; \end{array}$$

R₆ and R₇ taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-; or R₇ is -H and R₆ is
-H
-Ar₁,
-R₉,
-(CH₂)_{1,2,3}-T₁-R₉, or
an α-amino acid side chain residue;

each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted with -OH, -F, or =O and optionally substituted with one or two Ar₁ groups;

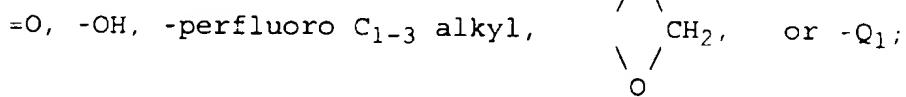
each R_{10} is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

each R₁₃ is independently selected from the group
 consisting of -Ar₂, -R₄ and -N-OH
 \
 R₅:

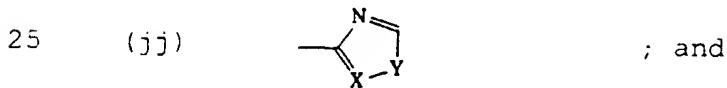
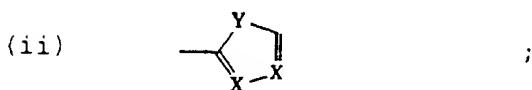
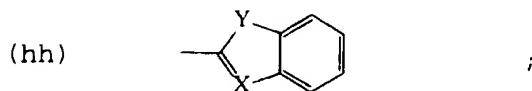
each Ar_1 is a cyclic group independently selected

- 33 -

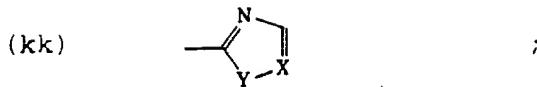
from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said 5 cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle 10 group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted with -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, 15



20 each Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ and -Q₂:



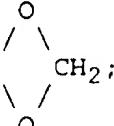
- 34 -



each Q_1 is independently selected from the group consisting of:

- Ar_1
- 5 - $O-Ar_1$
- R_9 ,
- T_1-R_9 , and
- $(CH_2)_{1,2,3}-T_1-R_9$;

10 each Q_2 is independently selected from the group consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I,

- NO₂, -CN, -CF₃, and
- 15 

provided that when - Ar_1 is substituted with a Q_1 group which comprises one or more additional - Ar_1 groups, said additional - Ar_1 groups are not substituted
20 with Q_1 ;

each X is independently selected from the group consisting of =N-, and =CH-;

each X_2 is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

25 each X_3 is independently selected from the group consisting of -CH₂-, -S-, -SO-, and -SO₂-;

each X_4 is independently selected from the group consisting of -CH₂- and -NH-;

- 35 -

each X_5 is independently selected from the group consisting of $-CH-$ and $-N-$;

| |

X_6 is $-CH-$ or $-N-$;

5 each Y is independently selected from the group consisting of $-O-$, $-S-$, and $-NH$;

each Z is independently CO or SO_2 ;

each a is independently 0 or 1;

each c is independently 1 or 2; ...

10 each d is independently 0, 1, or 2; and

each e is independently 0, 1, 2, or 3;

provided that when

R₁ is (f),

15 R₆ is an α -amino acid side chain residue, and
R₇ is -H,

then (aa1) and (aa2) must be substituted with Q₁;

also provided that when

20 R₁ is (o),
g is 0,
J is -H,
m is 1,

25 R₆ is an α -amino acid side chain residue,
R₇ is -H,

X₂ is $-CH_2-$,

X₅ is $-CH-$,
|

30 X₆ is $-N-$, and
|

R₃ is $\begin{array}{c} /R_{10} \\ -CO-N \\ \backslash R_{10} \end{array}$, or $-CO-R_{13}$, when

- 36 -

R_{13} is:

- $CH_2-O-CO-Ar_1$,
- $CH_2-S-CO-Ar_1$,
- CH_2-O-Ar_1 ,
- CH_2-S-Ar_1 , or
- 5 - R_4 when $-R_4$ is -H;

then the ring of the $R_1(o)$ group must be substituted with Q_1 or benzofused; and

provided that when

- 10 R_1 is (w),
- g is 0,
- J is -H,
- m is 1,
- T is $-CO_2H$,
- 15 X_2 is O,
- R_5 is benzyloxycarbonyl, and
- ring C is benzo,

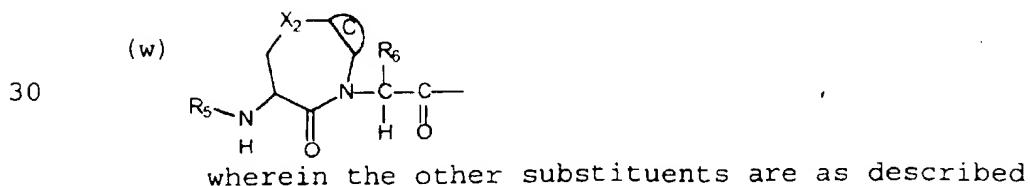
then R_3 cannot be $-CO-R_{13}$ when:

- 20 R_{13} is $-CH_2-O-Ar_1$ and
- Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom;

or when

- 25 R_{13} is $-CH_2-O-CO-Ar_1$, wherein
- Ar_1 is 2,6-dichlorophenyl.

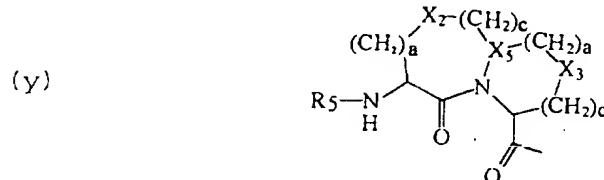
Preferred compounds of embodiment A employ formula α , wherein R_1 is (w):



- 37 -

above.

Other preferred compounds of embodiment A employ formula α , wherein R_1 is (y):



5 wherein the other substituents are as described above.

More preferred compounds of embodiment A employ formula α , wherein:

X_1 is -CH;

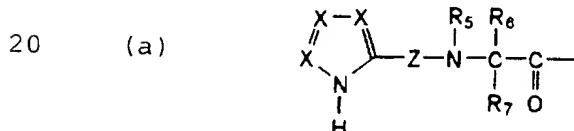
10 g is 0;

J is -H;

m is 0 or 1 and T is -CO-CO₂H, or any bioisosteric replacement for -CO₂H, or

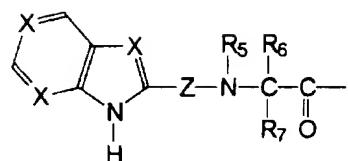
m is 1 and T is -CO₂H;

15 R₁ is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q₁, at any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H, or halogen, and wherein (e) is optionally benzofused:

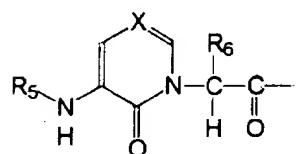


- 38 -

(b)

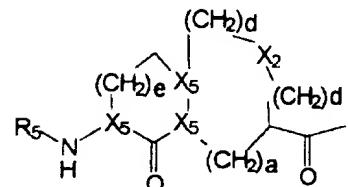


(c)

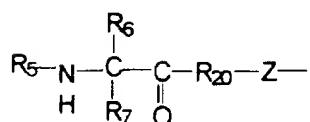


5

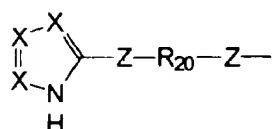
(e)



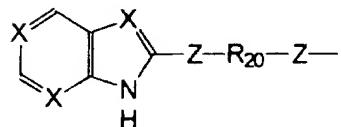
(f)



(g)

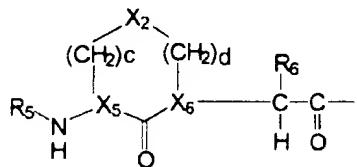


(h)



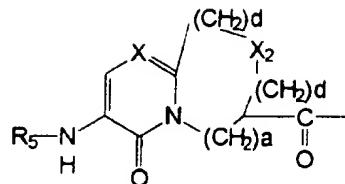
10

(o)



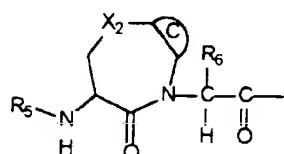
- 39 -

(r)

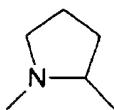


, and

(w)

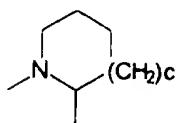
5 R₂₀ is:

(aa1)



, or

(aa2)



and c is 1;

10 ring C is benzo optionally substituted with
-C₁₋₃ alkyl, -O-C₁₋₃ alkyl, -Cl, -F or -CF₃;when R₁ is (a) or (b), R₅ is preferably -H, and15 when R₁ is (c), (e), (f), (o), (r), (w), (x) or
(y), R₅ is preferably:-CO-Ar₁-SO₂-Ar₁,-CO-NH₂,-CO-NH-Ar₁20 -CO-R₉,-CO-O-R₉,

- 40 -

-SO₂-R₉, or

-CO-NH-R₉,

R₇ is -H and R₆ is: -H,

-R₉, or

-Ar₁;

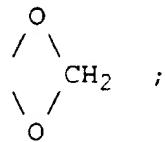
5

R₉ is a C₁₋₆ straight or branched alkyl group
optionally substituted with =O and optionally
substituted with -Ar₁;

R₁₀ is -H or a -C₁₋₃ straight or branched alkyl
10 group;

Ar₁ is phenyl, naphthyl, pyridyl, benzothiazolyl,
thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or
indolyl optionally substituted with -O-C₁₋₃ alkyl, -NH-
C₁₋₃ alkyl, -N-(C₁₋₃ alkyl)₂, -Cl, -F, -CF₃,

15 -C₁₋₃ alkyl, or



20 Q₁ is R₉ or -(CH₂)_{0,1,2}-T₁-(CH₂)_{0,1,2}-Ar₁, wherein
T₁ is -O- or -S-;

each X is independently selected from the group
consisting of =N-, and =CH-;

25 each X₂ is independently selected from the group
consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

each X₅ is independently selected from the group
consisting of -CH- and -N-;

30

X₆ is -CH- or -N-,

- 41 -

provided that when:

R_1 is (o),

X_2 is $-CH_2-$,

X_5 is $-CH-$, and

5

X_6 is $-N-$,

|

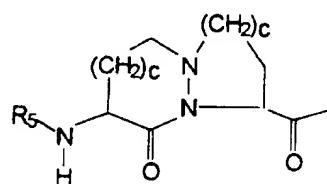
then the ring of the $R_1(o)$ group must be
10 substituted with Q_1 or benzofused; and

Z is C=O.

Most preferably, compounds of this more preferred embodiment are those wherein the R_1 group is:

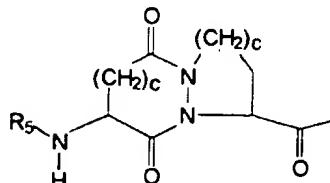
(e1)

15



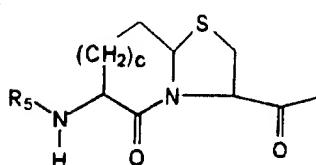
, or

(e2)



and c is 2; or

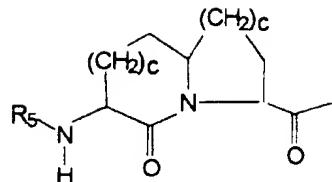
(e4)



, or

- 42 -

(e7)



which is optionally benzofused,
and c is 1 or 2;

provided that when R₁ is (e4),

5 g is 0,
 J is -H,
 m is 1,
 T is -CO₂H,
 R₅ is benzyloxycarbonyl, and
 10 c is 1,

then R₃ cannot be -CO-R₁₃ when
 R₁₃ is -CH₂-O-Ar₁ and
 Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-
 5-yl, wherein the phenyl is optionally substituted with
 15 a chlorine atom; or when

R₁₃ is -CH₂-O-CO-Ar₁, wherein
 Ar₁ is 2,6-dichlorophenyl,
 and when the 2-position of the scaffold ring is
 20 substituted with para-fluoro-phenyl; and

also provided that when
 R₁ is (e7),
 g is 0,
 J is -H,
 m is 1,
 T is -CO₂H or -CO-NH-OH,
 R₅ is a protective group for the N atom of an
 amino acid side chain residue, and
 each c is 1,

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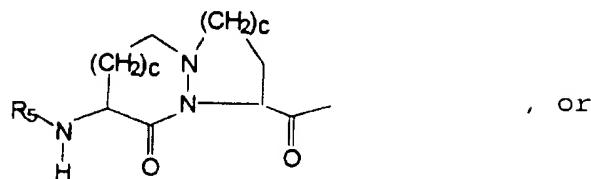
then R_3 cannot be $-CO-R_{13}$ when
 R_{13} is:

- CH₂-O-CO-Ar₁,
- CH₂-S-CO-Ar₁,
- 5 -CH₂-O-Ar₁, or
- CH₂-S-Ar₁.

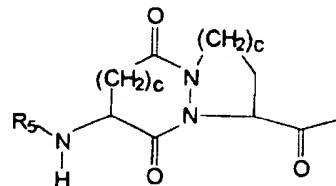
The most preferred compounds of this embodiment are those wherein:

R_1 is:

10 (e1)



(e2)



and c is 2;

m is 1;

15 T is $-CO_2H$; and

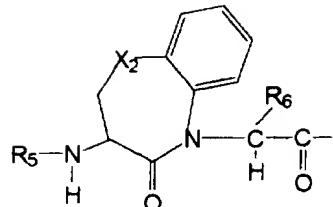
R_3 is $-CO-R_{13}$.

Other most preferred compounds of this embodiment are those wherein:

R_1 is:

- 44 -

(w1)



; wherein

X₂ is:

-O-,

5 -S-,

-SO₂-, or

-NH-;

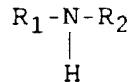
optionally substituted with R₅ or Q₁ at X₂ when X₂
10 is -NH-; and

ring C is benzo substituted with -C₁₋₃ alkyl,
-O-C₁₋₃ alkyl, -Cl, -F or -CF₃.

The ICE inhibitors of another embodiment (B)
of this invention are those of formula (I):

15

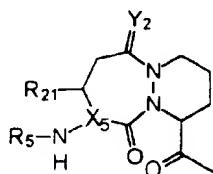
(I)



wherein:

R₁ is selected from the group consisting of the
20 following formulae:

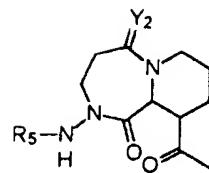
(e10)



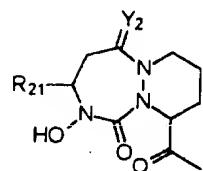
;

- 45 -

(e11)

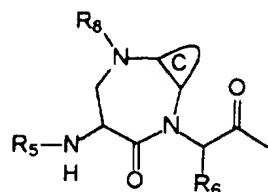


(e12)

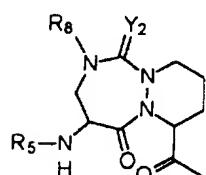


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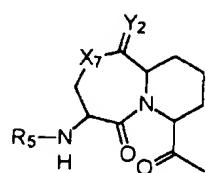
(w2)



(y1)

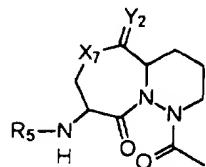


(y2)



10

(z)

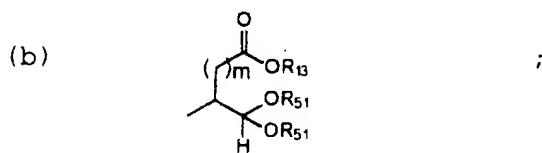
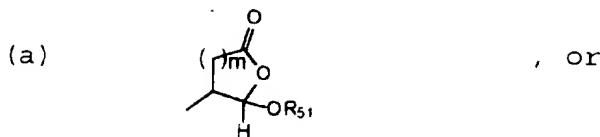


; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

- 46 -

R₂ is:

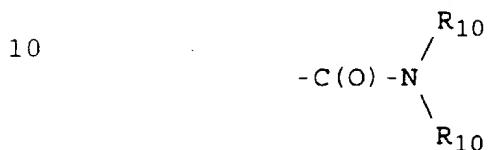


m is 1 or 2;

5

R₅ is selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,



- S(O)₂-R₉,
- C(O)-CH₂-O-R₉,
- C(O)C(O)-R₁₀,
- R₉,
- H, and
- C(O)C(O)-OR₁₀;

20 X₅ is -CH- or -N-;

Y₂ is H₂ or O;

X₇ is -N(R₈)- or -O-;

25

- 47 -

R₆ is selected from the group consisting of -H and -CH₃;

R₈ is selected from the group consisting of:

5

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(H)-R₁₀,
- S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- 10 -C(O)-CH₂-OR₁₀,
- C(O)C(O)-R₁₀;
- C(O)-CH₂N(R₁₀)(R₁₀) ,
- C(O)-CH₂C(O)-O-R₉,
- C(O)-CH₂C(O)-R₉,
- 15 -H, and
- C(O)-C(O)-OR₁₀;

15

each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

20

each R₁₀ is independently selected from the group consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

25

R₁₃ is selected from the group consisting of H, Ar₃, and a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

- 48 -

each R₅₁ is independently selected from the group consisting of R₉, -C(O)-R₉, -C(O)-N(H)-R₉, or each R₅₁ taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

5 each R₂₁ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains 10 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-, 15 said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

20 each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, -NHR₉, R₉, -C(O)-R₁₀, and



30 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

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Preferably, R₅ is selected from the group consisting of:

- 5 -C(O)-R₁₀,
 -C(O)O-R₉, and
 -C(O)-NH-R₁₀.

Alternatively, R₅ is selected from the group consisting of:

- 10 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-C(O)-R₁₀,
 -R₉, and
 -C(O)-C(O)-OR₁₀.

More preferably:

m is 1;

15 R₁₃ is H or a -C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

20 R₂₁ is -H or -CH₃;

R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

25 Ar₃ is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

- 50 -

each Q_1 is independently selected from the group consisting of $-\text{NH}_2$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OH}$, $-\text{R}_9$, $-\text{NH}-\text{R}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$ or $-\text{S}(\text{O})_2-\text{R}_9$, $-\text{OR}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$, $-\text{OR}_9$, $-\text{NHR}_9$, and

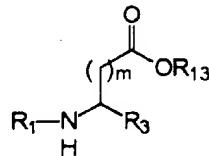


10 wherein each R_9 and R_{10} are independently a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

15 provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$.

The ICE inhibitors of another embodiment (C) of this invention are those of formula (II):

20 (II)



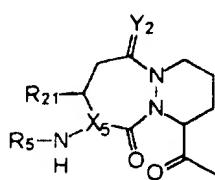
wherein:

m is 1 or 2;

R_1 is selected from the group consisting of the following formulae:

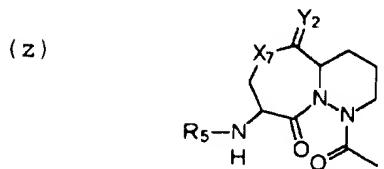
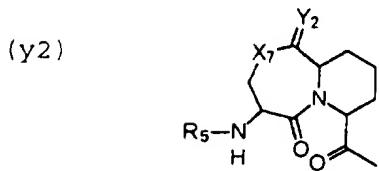
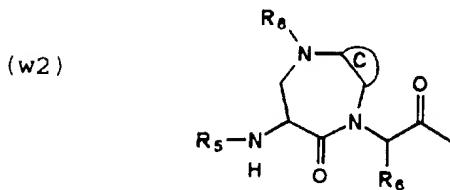
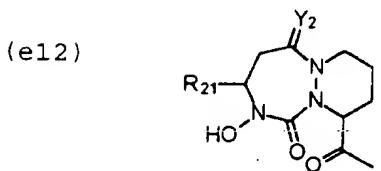
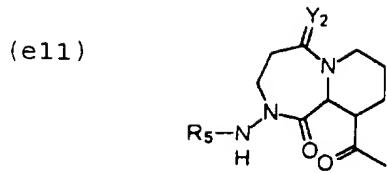
25

(e10)



;

- 51 -



10 ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

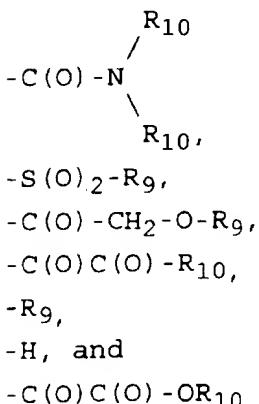
- 52 -

R₃ is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH₂-T₁-R₁₁,
- C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

R₅ is selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,



X₅ is -CH- or -N-;

25 Y₂ is H₂ or O;

X₇ is -N(R₈)- or -O-;

each T₁ is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

30 R₆ is selected from the group consisting of -H and -CH₃;

R₈ is selected from the group consisting of:

- 53 -

-C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-NH-R₁₀,
-S(O)₂-R₉,
5 -S(O)₂-NH-R₁₀,
-C(O)-CH₂-OR₁₀,
-C(O)C(O)-R₁₀,
-C(O)-CH₂-N(R₁₀)(R₁₀),
-C(O)-CH₂C(O)-O-R₉,
10 -C(O)-CH₂C(O)-R₉,
-H, and
-C(O)-C(O)-OR₁₀;

each R₉ is independently selected from the group
consisting of -Ar₃ and a -C₁₋₆ straight or branched
15 alkyl group optionally substituted with Ar₃, wherein
the -C₁₋₆ alkyl group is optionally unsaturated;

each R₁₀ is independently selected from the group
consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a
-C₁₋₆ straight or branched alkyl group optionally
20 substituted with Ar₃, wherein the -C₁₋₆ alkyl group is
optionally unsaturated;

each R₁₁ is independently selected from the group
consisting of:

-Ar₄,
25 -(CH₂)₁₋₃-Ar₄,
-H, and
-C(O)-Ar₄;

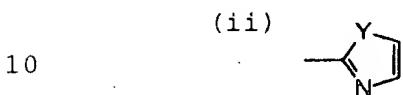
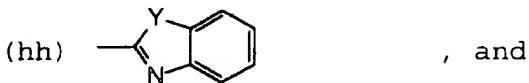
R₁₃ is selected from the group consisting of H,
Ar₃, and a C₁₋₆ straight or branched alkyl group
30 optionally substituted with Ar₃, -CONH₂, -OR₅, -OH,
-OR₉, or -CO₂H;

- 54 -

-OR_{13} is optionally -N(H)-OH ;

each R_{21} is independently selected from the group consisting of -H or a -C_{1-6} straight or branched alkyl group;

5 Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q_1 :



wherein each Y is independently selected from the group consisting of O and S ;

15 each Ar_3 is a cyclic group independently selected fr. the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom 20 group selected from -O- , -S- , -SO- , SO_2 , $=\text{N-}$, and -NH- , $\text{-N(R}_5\text{)}-$, and $\text{-N(R}_9\text{)}-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1 ;

25 each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and

- 55 -

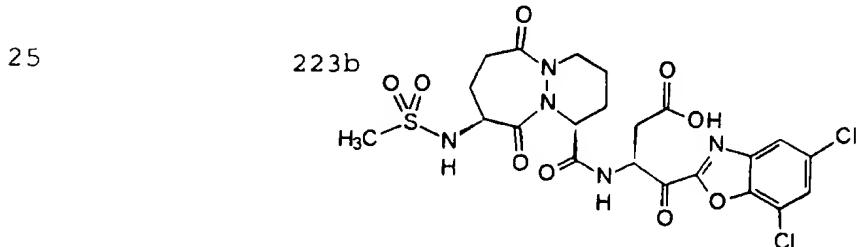
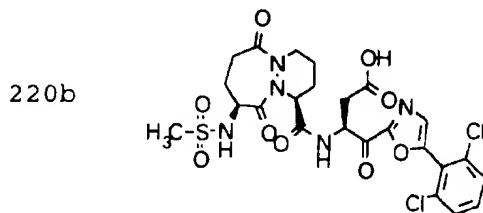
15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, 5 and said cyclic group optionally being singly or multiply substituted by -Q₁:

each Q₁ is independently selected from the group 10 consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, -NHR₉, R₉, -C(O)-R₁₀, and

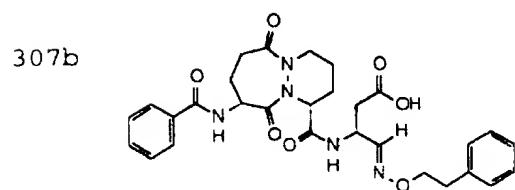
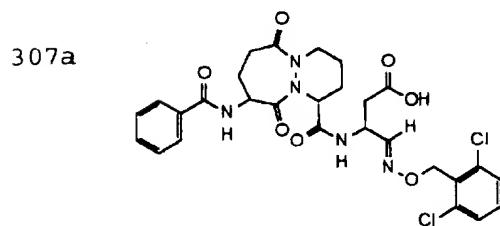
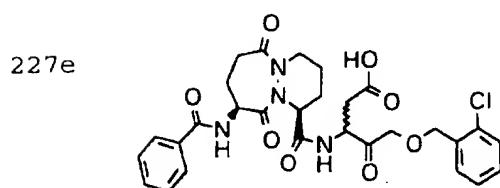
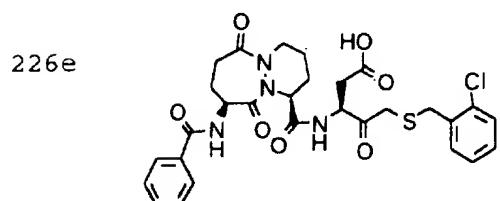
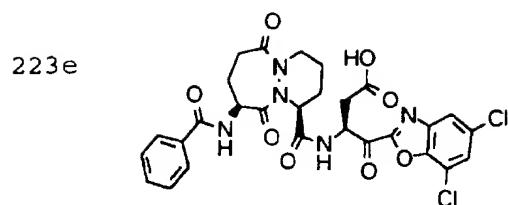


provided that when -Ar₃ is substituted with a Q₁ 20 group which comprises one or more additional -Ar₃ with another -Ar₃.

Preferred compounds of this embodiment include, but are not limited to:

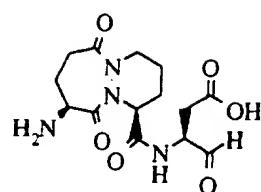


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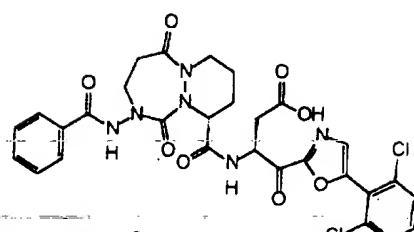


- 57 -

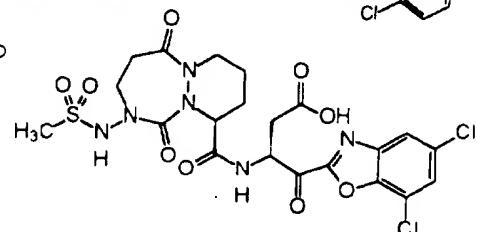
429



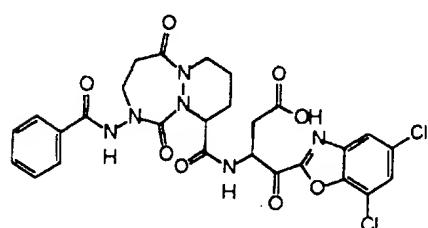
820b



823b

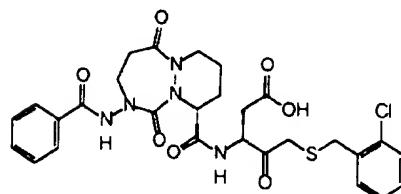


823e

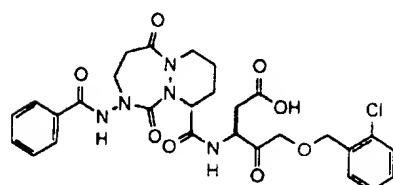


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826e

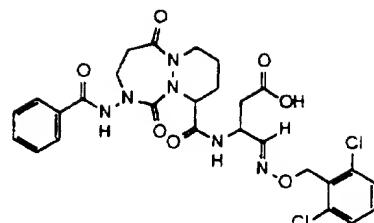


827e

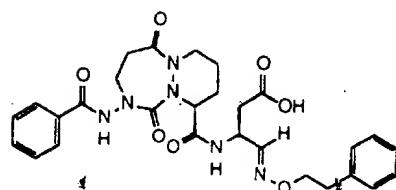


- 58 -

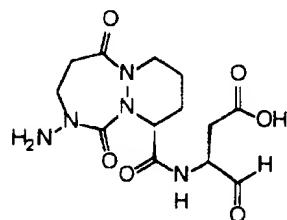
907a



907b



1029



Preferred compounds of embodiment C employ
5 formula (II), wherein R₁ is (e11) and the other
substituents are as defined above.

Other preferred compounds of embodiment C
employ formula (II), wherein R₁ is (e12) and the other
substituents are as defined above.

10 Other preferred compounds of embodiment C
employ formula (II) wherein R₁ is (y1) and the other
substituents are as defined above.

15 Other preferred compounds of embodiment C
employ formula (II) wherein R₁ is (y2) and the other
substituents are as defined above.

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Other preferred compounds of embodiment C of employ formula (II) wherein R₁ is (z) and the other substituents are as defined above.

5 Other preferred compound of embodiment C employ formula (II) wherein R₁ is (w2) and the other substituents are as defined above.

More preferably, R₁ is (w2) and

m is 1;

ring C is benzo, pyrido, or thieno;

10 R₃ is selected from the group consisting of -C(O)-H, -C(O)-Ar₂, and -C(O)CH₂-T₁-R₁₁;

R₅ is selected from the group consisting of:

-C(O)-R₁₀, wherein R₁₀ is -Ar₃;

-C(O)O-R₉, wherein R₉ is -CH₂-Ar₃;

15 -C(O)C(O)-R₁₀, wherein R₁₀ is -CH₂Ar₃;

-R₉, wherein R₉ is a C₁₋₂ alkyl group substituted with -Ar₃; and

-C(O)C(O)-OR₁₀, wherein R₁₀ is -CH₂Ar₃;

20 T₁ is O or S;

R₆ is H;

R₈ is selected from the group consisting -C(O)-R₁₀, -C(O)-CH₂-OR₁₀, and -C(O)CH₂-N(R₁₀)(R₁₀), wherein R₁₀ is H, CH₃, or -CH₂CH₃;

25 R₁₁ is selected from the group consisting of -Ar₄, -(CH₂)₁₋₃-Ar₄, and -C(O)-Ar₄;

- 60 -

R₁₃ is H or a -C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl,
5 wherein the phenyl is optionally substituted with Q₁;

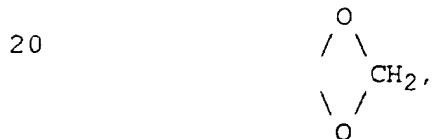
Ar₂ is (hh);

Y is O;

Ar₃ is phenyl, naphthyl, thienyl, quinolinyl,
10 isoquinolinyl, thiazolyl, benzimidazolyl,
thienothienyl, thiadiazolyl, benzotriazolyl,
benzo[b]thiophenyl, benzofuranyl, and indolyl;

Ar₄ is phenyl, tetrazolyl, naphthyl, pyridinyl,
oxazolyl, pyrimidinyl, or indolyl;

15 each Q₁ is independently selected from the group
consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
-C(O)-R₁₀, -OR₉, -NHR₉, and

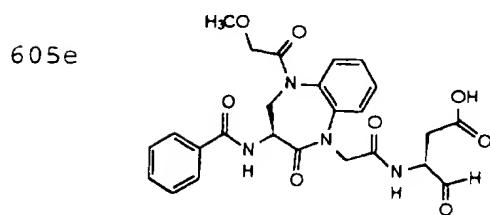
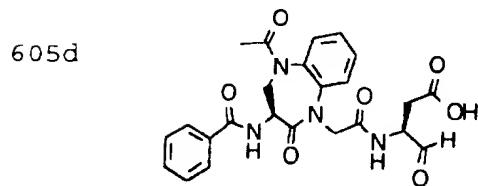
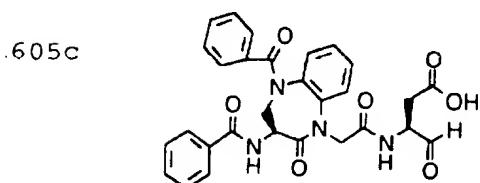
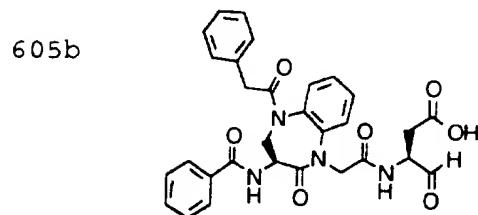
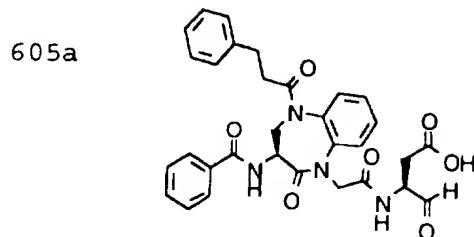


wherein each R₉ and R₁₀ are independently a -C₁₋₆
25 straight or branched alkyl group optionally substituted
with Ar₃ wherein Ar₃ is phenyl;

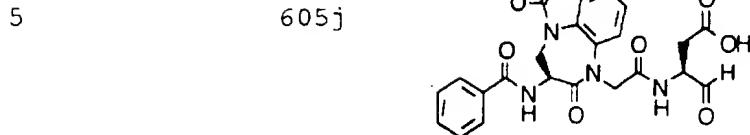
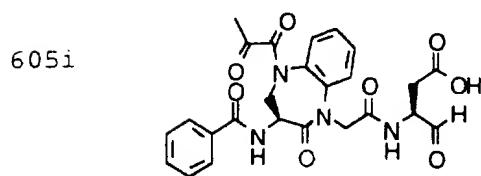
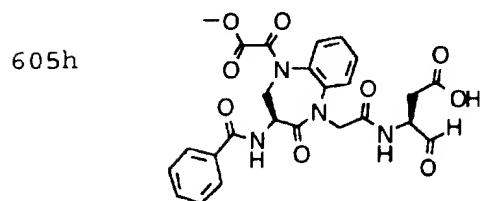
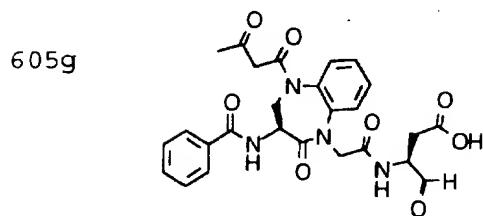
provided that when -Ar₃ is substituted with a Q₁
group which comprises one or more additional -Ar₃
30 groups, said additional -Ar₃ groups are not substituted
with another -Ar₃.

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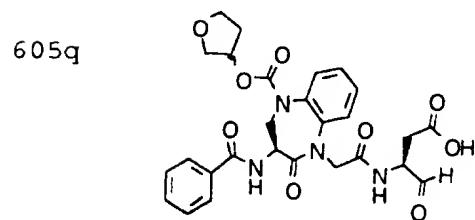
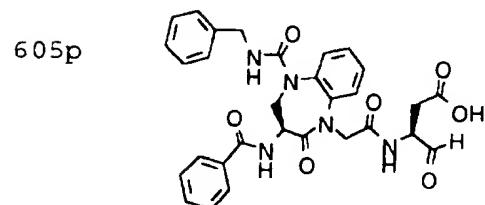
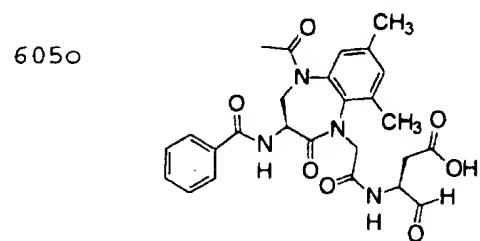
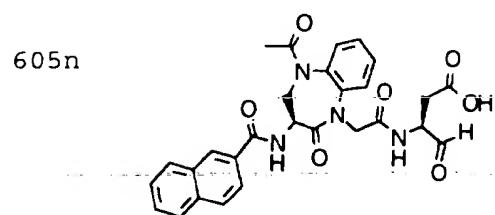
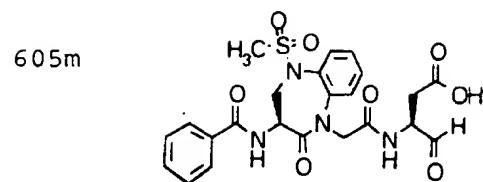
Preferred compounds of this embodiment include, but are not limited to:



- 62 -

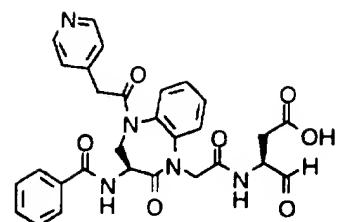


- 63 -

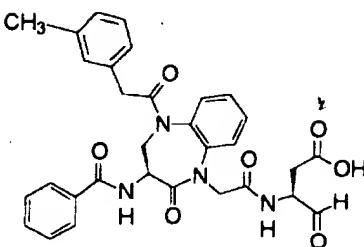


- 64 -

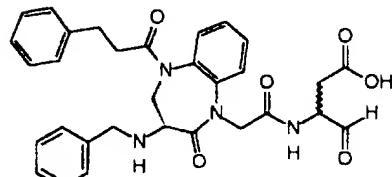
605s



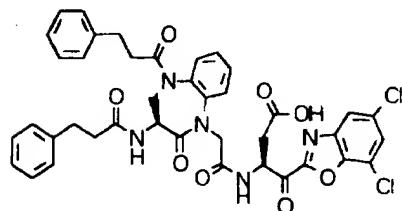
605t



605v

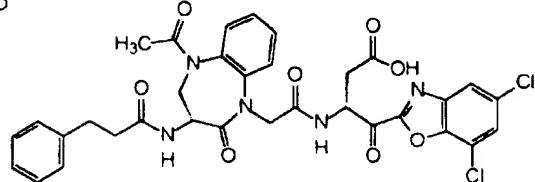


609a



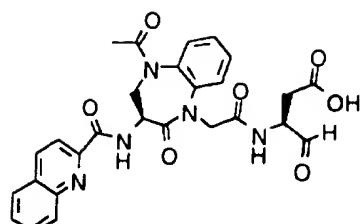
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609b

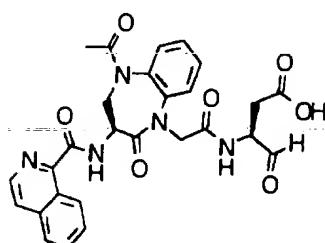


- 65 -

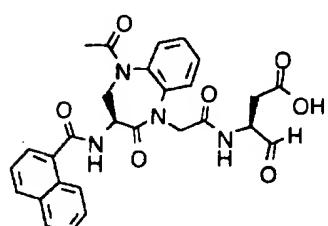
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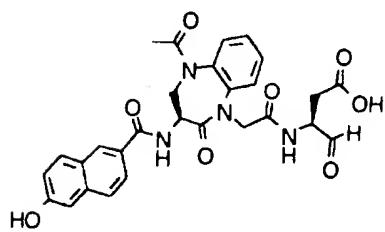
620



621

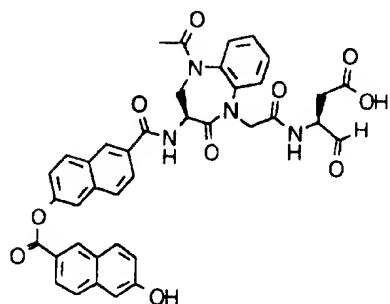


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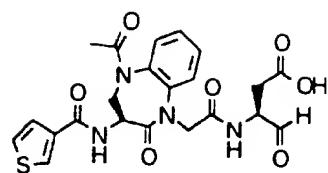
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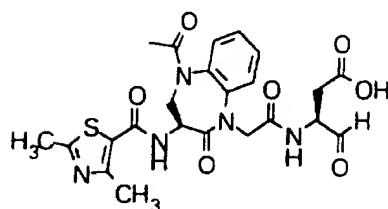


- 66 -

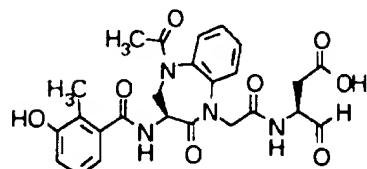
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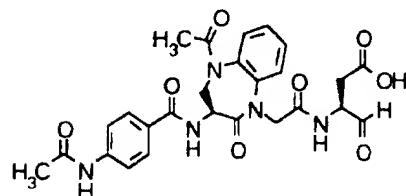
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626

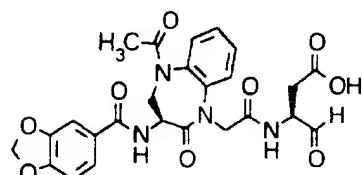


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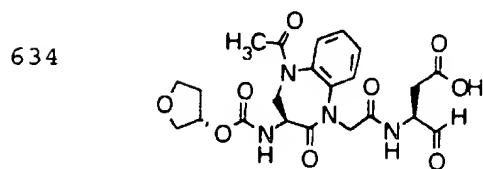
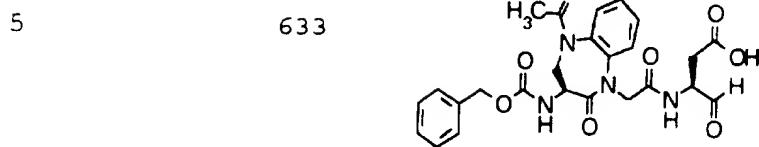
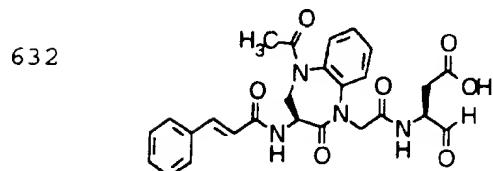
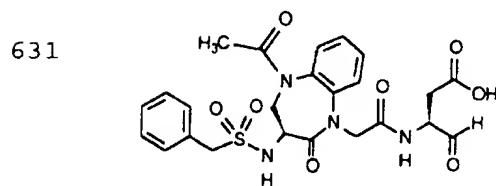
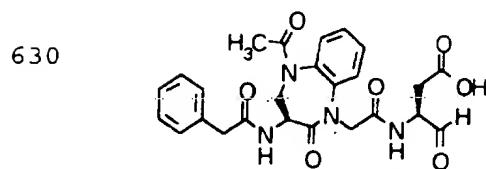
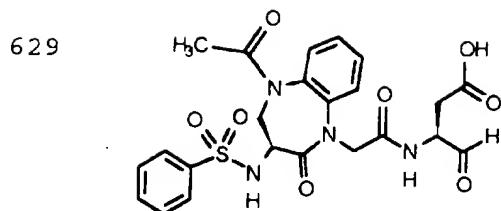


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628



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635



Other preferred compounds of embodiment C employ formula (II) wherein R₁ is (e10), X₅ is CH, and 5 the other substituents are as defined above.

More preferred compounds of embodiment C employ formula (II) wherein R₁ is (e10), X₅ is CH, R₃ is CO-Ar₂, and the other substituents are as defined above.

10 Other more preferred compounds of embodiment C employ formula (II) wherein R₁ is (e10), X₅ is CH, R₃ is -C(O)-CH₂-T₁-R₁₁, R₁₁ is -(CH₂)₁₋₃-Ar₄, and the other substituents are as defined above.

15 Other more preferred compounds of embodiment C employ formula (II) wherein R₁ is (e10) and X₅ is CH and

R₃ is -C(O)-CH₂-T₁-R₁₁;
T₁ is O; and
R₁₁ is -C(O)-Ar₄,

20 and the other substituents are as defined above.

More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉, and
25 -C(O)-NH-R₁₀.

- 69 -

Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

- 5 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-C(O)-R₁₀,
 -R₉, and
 -C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds,

m is 1;

10

T₁ is O or S;

15 R₁₃ is H or a -C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

R₂₁ is -H or -CH₃;

20 R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

Ar₂ is (hh);

Y is O, and

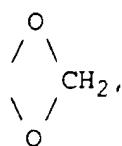
25 Ar₃ is phenyl, naphthyl, thiienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

- 70 -

Ar_4 is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

each Q_1 is independently selected from the group consisting of $-\text{NH}_2$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OH}$, $-\text{R}_9$, $-\text{NH}-\text{R}_5$

5 wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$ or $-\text{S}(\text{O})_2-\text{R}_9$, $-\text{OR}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$, $-\text{OR}_9$, $-\text{NHR}_9$, and



wherein each R_9 and R_{10} are independently a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

15

provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$.

20

Other more preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3 is $-\text{C}(\text{O})-\text{H}$, and the other substituents are as defined above.

25

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

- $\text{C}(\text{O})-\text{R}_{10}$,
- $\text{C}(\text{O})\text{O}-\text{R}_9$, and
- $\text{C}(\text{O})-\text{NH}-\text{R}_{10}$.

30

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

- $\text{S}(\text{O})_2-\text{R}_9$,
- $\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$,

- 71 -

-C(O)-C(O)-R₁₀,

-R₉, and

-C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds,

5 m is 1;

T₁ is O or S;

R₁₃ is H or a -C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

R₂₁ is -H or -CH₃;

R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

Ar₂ is (hh);

Y is O, and

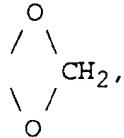
20 Ar₃ is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

25 Ar₄ is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

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each Q_1 is independently selected from the group consisting of $-\text{NH}_2$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OH}$, $-\text{R}_9$, $-\text{NH}-\text{R}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$ or $-\text{S}(\text{O})_2-\text{R}_9$, $-\text{OR}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$, $-\text{OR}_9$, $-\text{NHR}_9$, and

5



10 wherein each R_9 and R_{10} are independently a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

15 provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$,

20 Other more preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10) and X_5 is CH , R_3 is $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$, and R_{11} is $-\text{Ar}_4$, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

25 $-\text{C}(\text{O})-\text{R}_{10}$,
 $-\text{C}(\text{O})\text{O}-\text{R}_9$, and
 $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-\text{S}(\text{O})_2-\text{R}_9$,

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-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉, and
-C(O)-C(O)-OR₁₀.

5 Most preferably, in these more preferred compounds,

m is 1;

T₁ is O or S;

10 R₁₃ is H or a -C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

R₂₁ is -H or -CH₃;

15 R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

Ar₂ is (hh);

Y is O, and

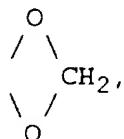
20 25 Ar₃ is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

Ar₄ is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

- 74 -

each Q_1 is independently selected from the group consisting of $-\text{NH}_2$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OH}$, $-\text{R}_9$, $-\text{NH}-\text{R}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$ or $-\text{S}(\text{O})_2-\text{R}_9$, $-\text{OR}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$, $-\text{OR}_9$, $-\text{NHR}_9$, and

5



10 wherein each R_9 and R_{10} are independently a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

15 provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$.

20 Other preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10), X_5 is N, and the other substituents are as defined above.

More preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is CO-Ar_2 , and the other substituents are as defined above.

25

Other more preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$, R_{11} is $-(\text{CH}_2)_{1-3}-\text{Ar}_4$, and the other substituents are as defined above.

30

Other more preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10) and X_5 is N and:

- 75 -

R₃ is -C(O)-CH₂-T₁-R₁₁;
T₁ is O; and
R₁₁ is -C(O)-Ar₄, and the other substituents are as defined above.

5 More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

10 Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
15 -R₉, and
-C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

20 -S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉, and
-C(O)-C(O)-OR₁₀.

m is 1;

25

T₁ is O or S;

30 R₁₃ is H or a -C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

- 76 -

R₂₁ is -H or -CH₃;

R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

5 Ar₂ is (hh);

Y is O, and

10 Ar₃ is phenyl, naphthyl, thiaryl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

Ar₄ is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

15 each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and



wherein each R₉ and R₁₀ are independently a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

30 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

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Other more preferred compounds of embodiment C, employ formula (II) wherein R₁ is (e10), X₅ is N, R₃ is -C(O)-H, and the other substituents are as defined above.

5 More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉, and
- C(O)-NH-R₁₀.

10 Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

- S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-C(O)-R₁₀,
- 15 -R₉, and
- C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds,

m is 1;

20 T₁ is O or S;

R₁₃ is H or a -C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, 25 wherein the phenyl is optionally substituted with Q₁;

R₂₁ is -H or -CH₃;

R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

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Ar_2 is (hh);

Y is O, and

5 Ar_3 is phenyl, naphthyl, thienyl, quinolinyl,
 isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl,
 benzotriazolyl, benzimidazolyl, thienothienyl,
 imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl
 benzofuranyl, and indolyl;

10 Ar_4 is phenyl, tetrazolyl, pyridinyl, oxazolyl,
 naphthyl, pyrimidinyl, or thienyl;

each Q_1 is independently selected from the group
 consisting of $-\text{NH}_2$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OH}$, $-\text{R}_9$, $-\text{NH}-\text{R}_5$
 wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$ or $-\text{S}(\text{O})_2-\text{R}_9$, $-\text{OR}_5$ wherein R_5 is
 $-\text{C}(\text{O})-\text{R}_{10}$, $-\text{OR}_9$, $-\text{NHR}_9$, and



20 wherein each R_9 and R_{10} are independently a $-\text{C}_{1-6}$
 straight or branched alkyl group optionally substituted
 with Ar_3 wherein Ar_3 is phenyl;

25 provided that when $-\text{Ar}_3$ is substituted with a Q_1
 group which comprises one or more additional $-\text{Ar}_3$
 groups, said additional $-\text{Ar}_3$ groups are not substituted
 with another $-\text{Ar}_3$.

30 Other more preferred compounds of embodiment
 C, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3
 is $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$, R_{11} is $-\text{Ar}_4$, and the other
 substituents are as defined above.

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More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉, and
- 5 -C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

- S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- 10 -C(O)-C(O)-R₁₀,
- R₉, and
- C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds

m is 1;

15

T₁ is O or S;

R₁₃ is H or a -C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight 20 alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

R₂₁ is -H or -CH₃;

R₅₁ is a C₁₋₆ straight or branched alkyl group 25 optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

Ar₂ is (hh);

Y is O, and

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Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl
5 benzofuranyl, and indolyl;

Ar_4 is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

each Q_1 is independently selected from the group consisting of $-\text{NH}_2$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OH}$, $-\text{R}_9$, $-\text{NH}-\text{R}_5$
10 wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$ or $-\text{S}(\text{O})_2-\text{R}_9$, $-\text{OR}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$, $-\text{OR}_9$, $-\text{NHR}_9$, and



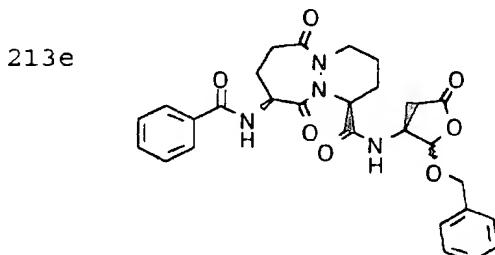
wherein each R_9 and R_{10} are independently a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

20

provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$.

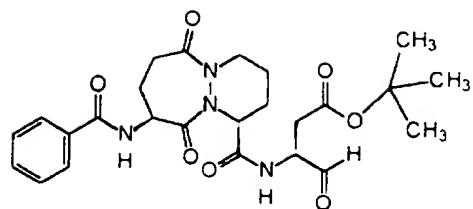
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Preferred compounds of embodiment B include, but are not limited to:

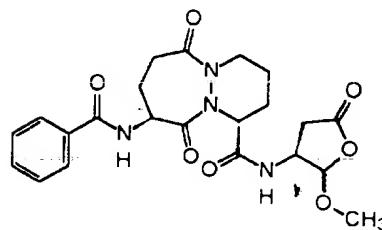


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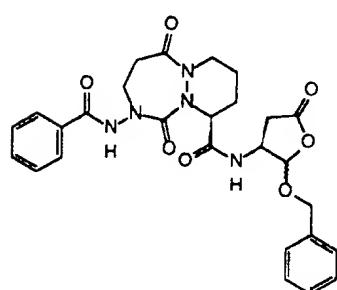
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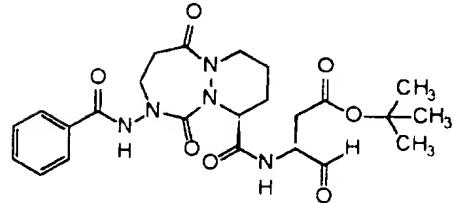
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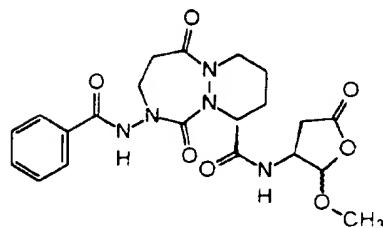


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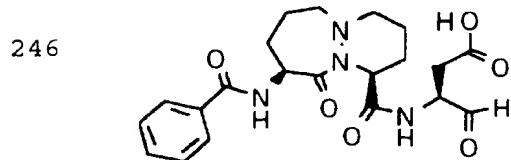
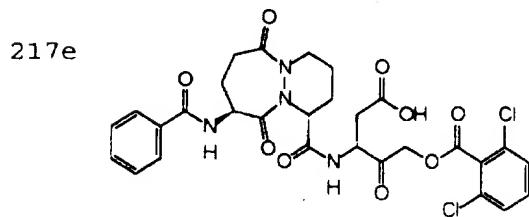
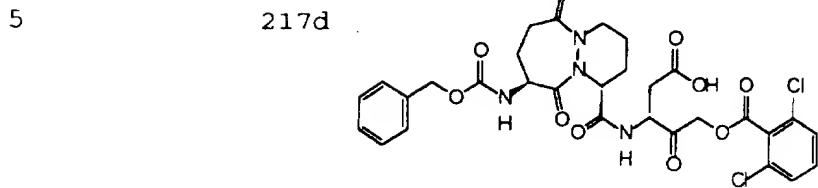
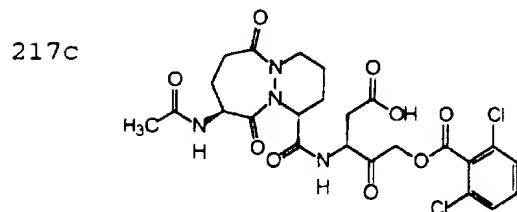
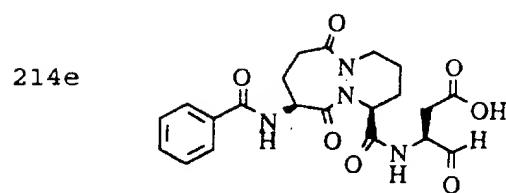
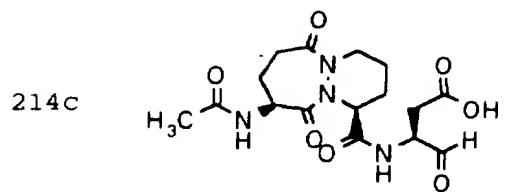
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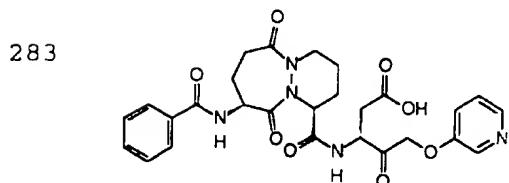
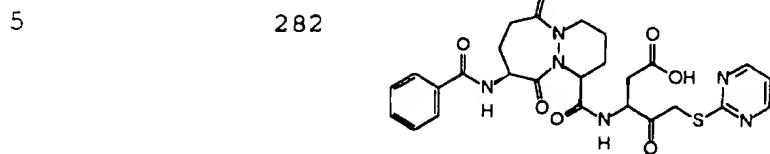
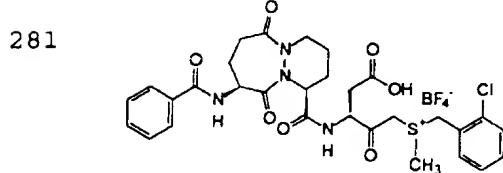
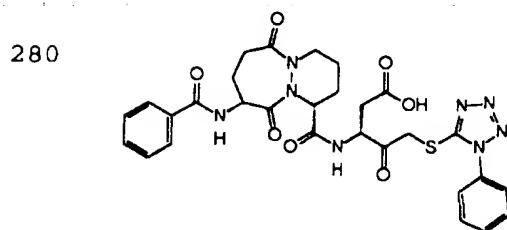
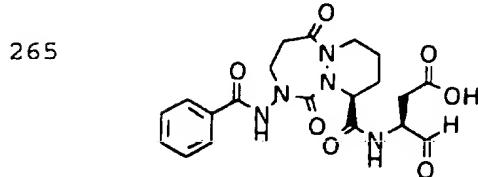
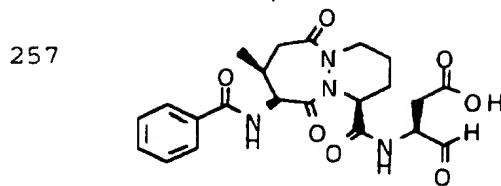


Preferred compounds of embodiment C include,
but are not limited to:

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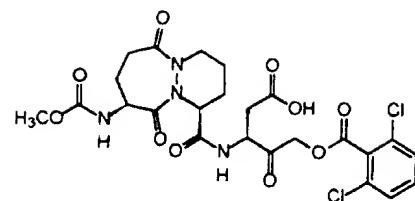


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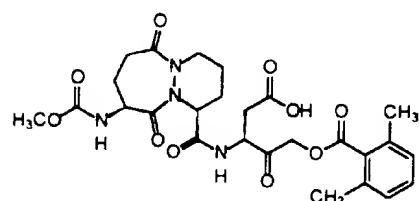


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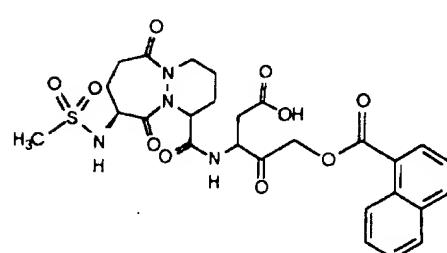
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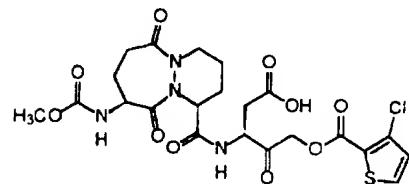
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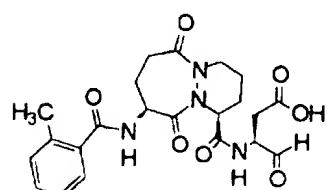


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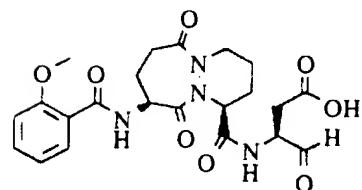


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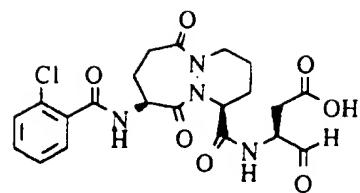


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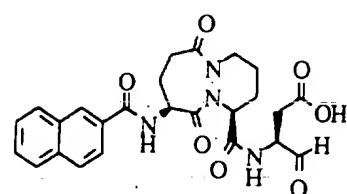


- 85 -

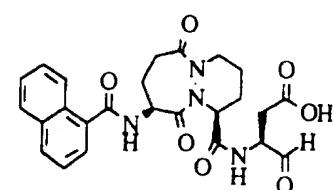
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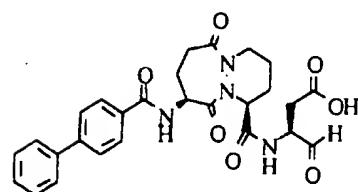
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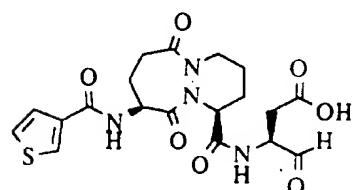


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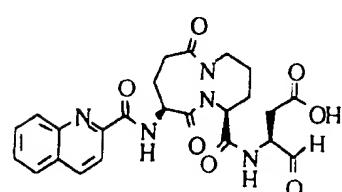


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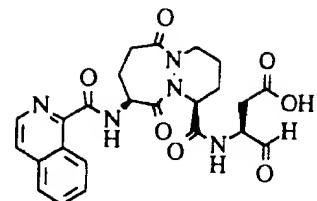


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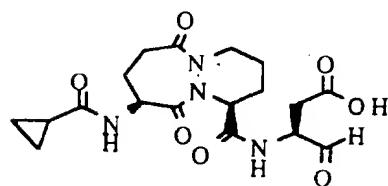


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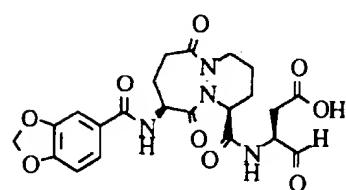
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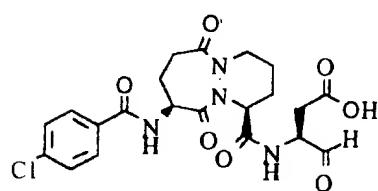
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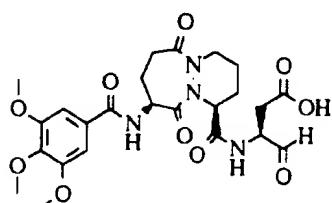


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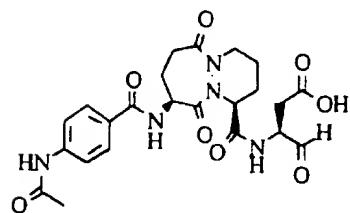


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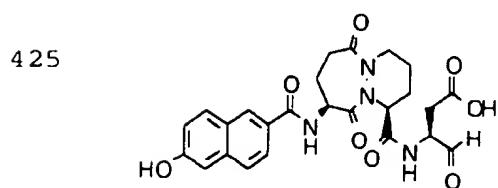
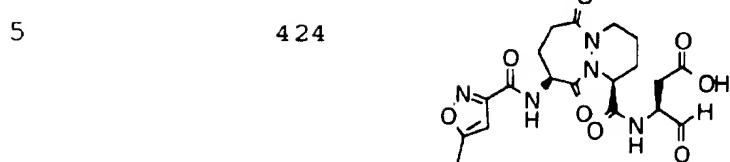
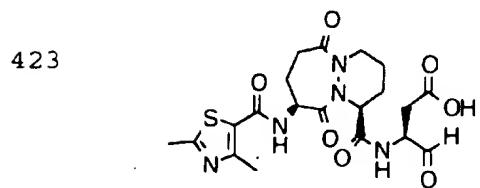
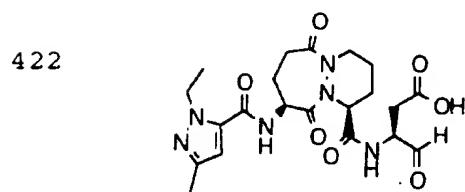
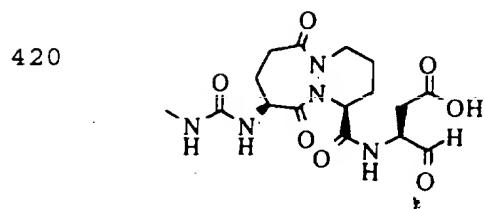
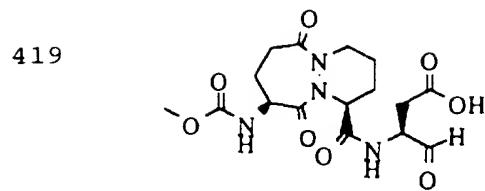
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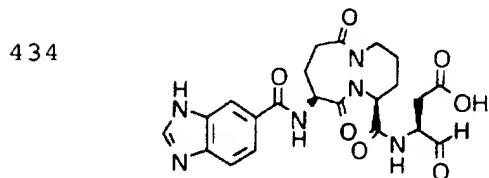
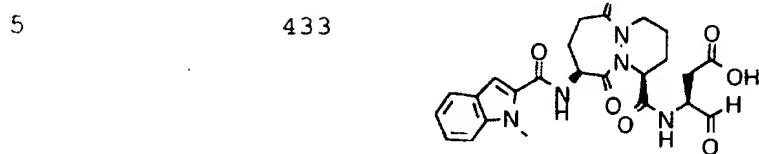
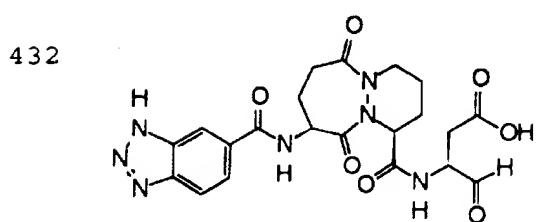
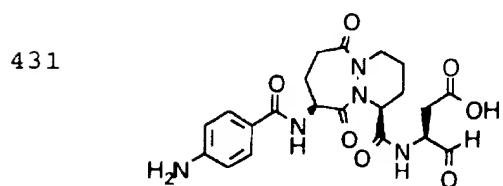
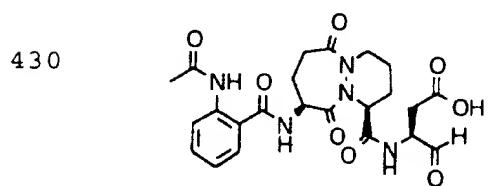
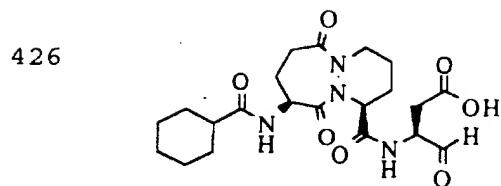
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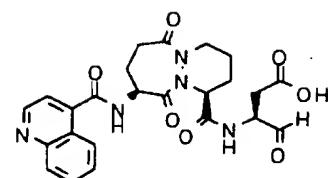


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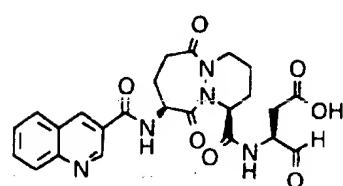


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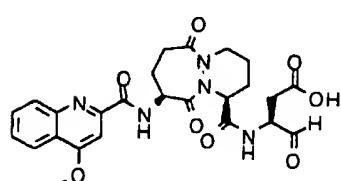
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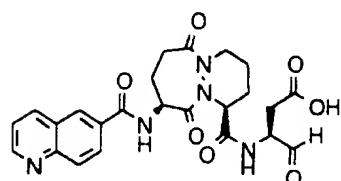
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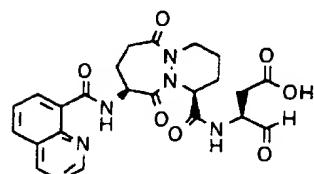


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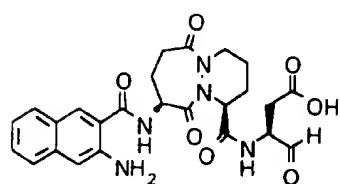


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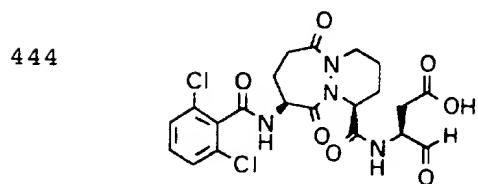
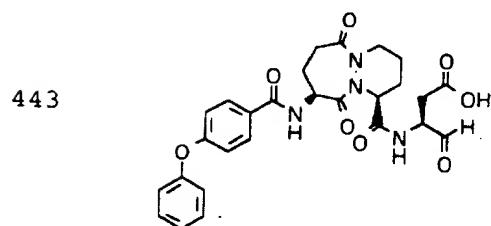
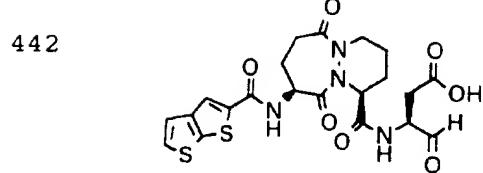
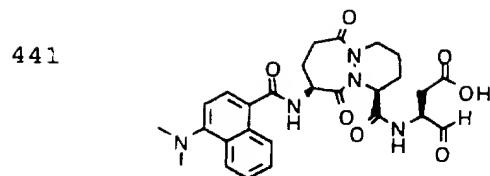
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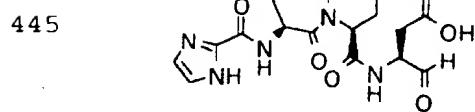
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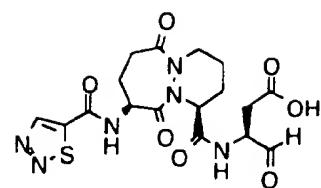


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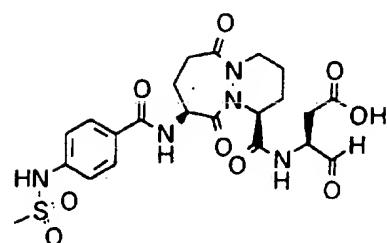


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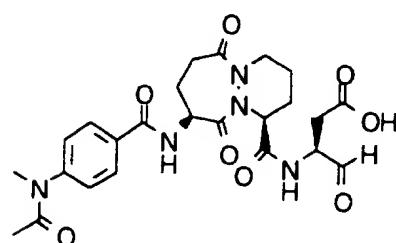
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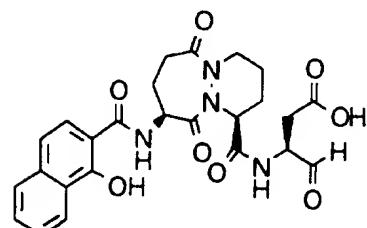
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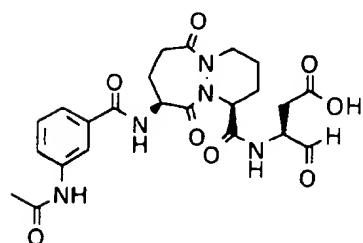


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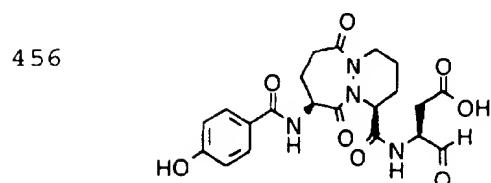
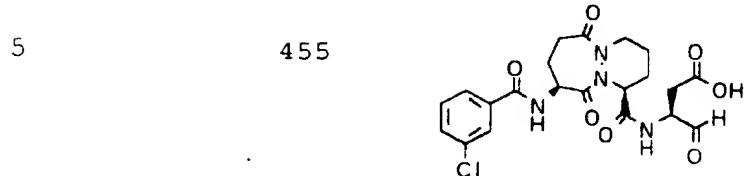
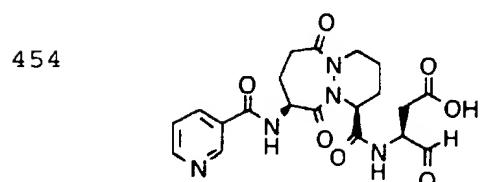
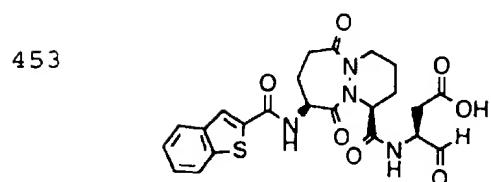
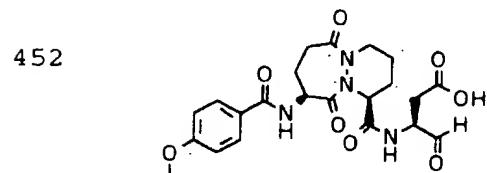
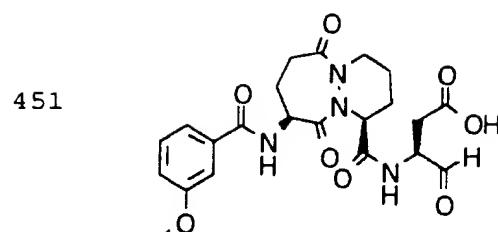


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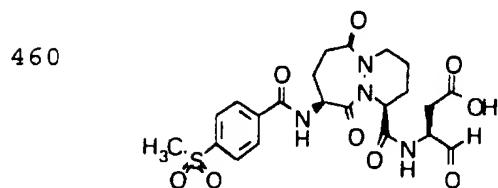
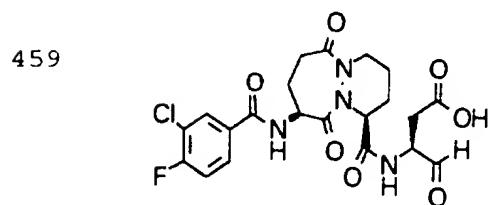
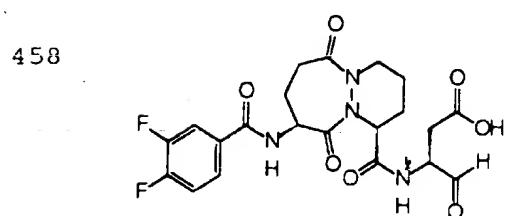
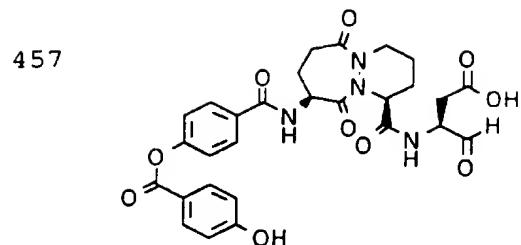
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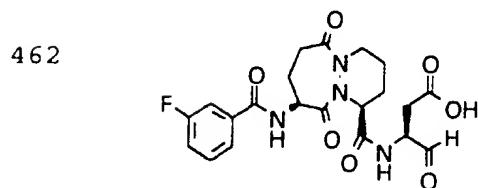
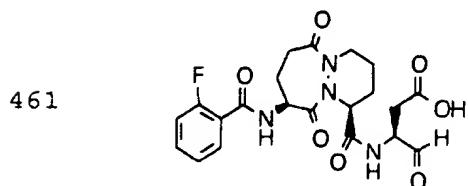
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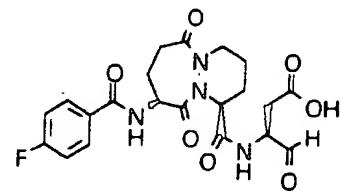


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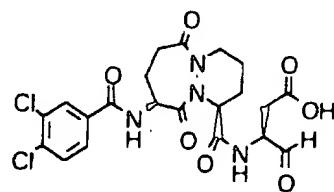


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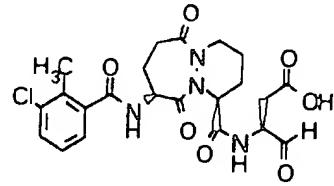
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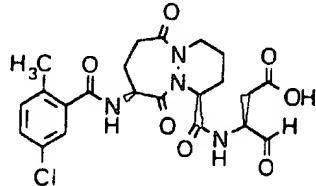
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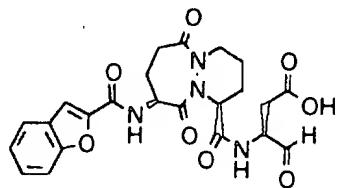


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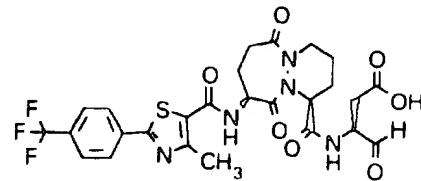


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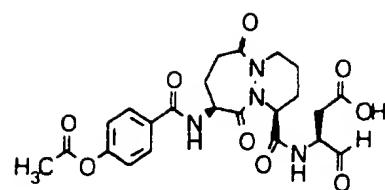


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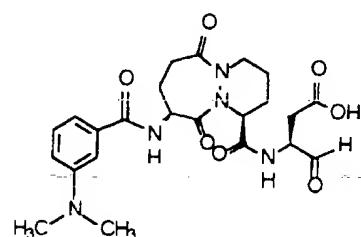


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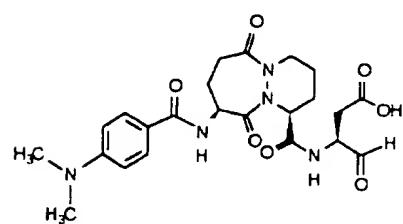
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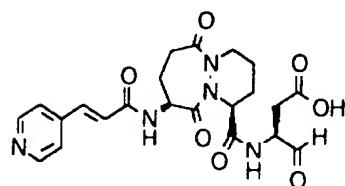
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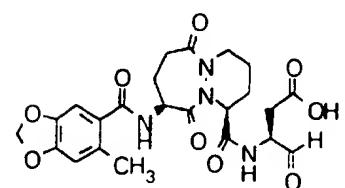


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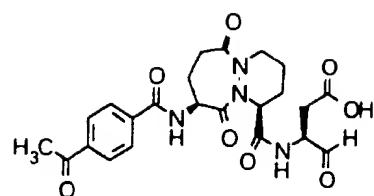
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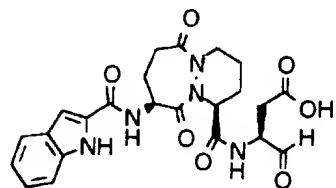


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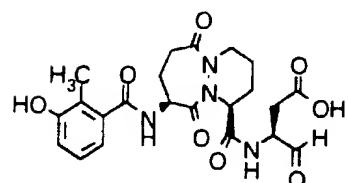
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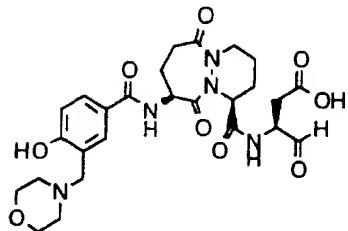
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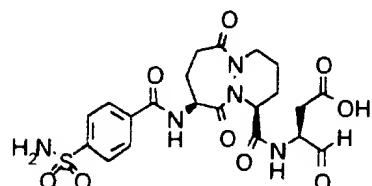


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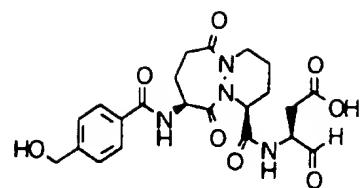
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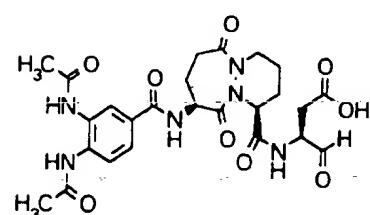


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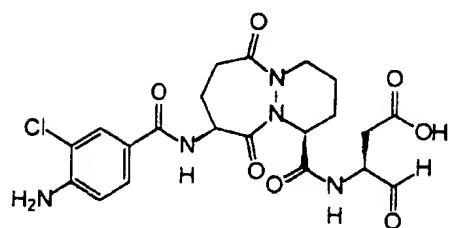
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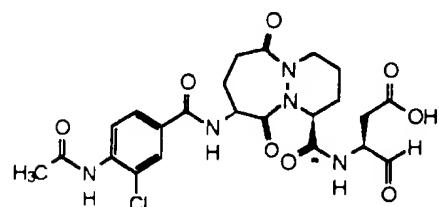
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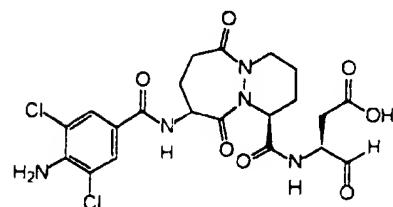


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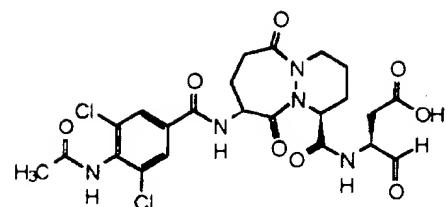
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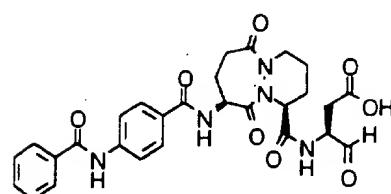


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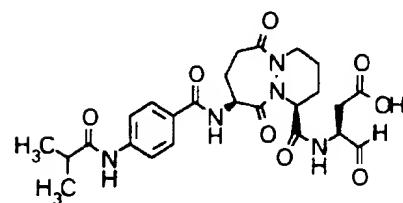
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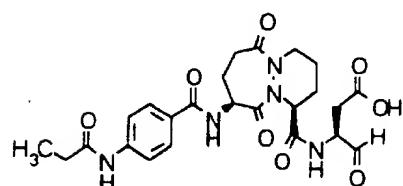
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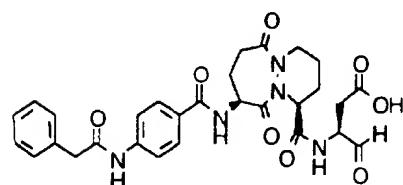


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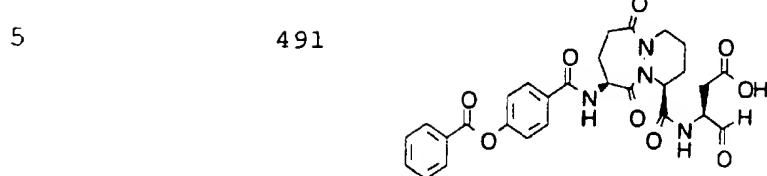
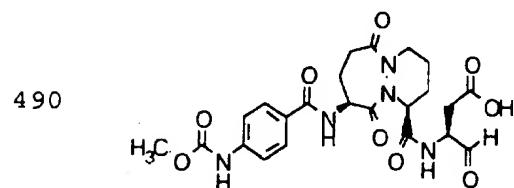
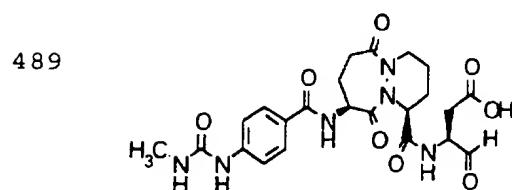
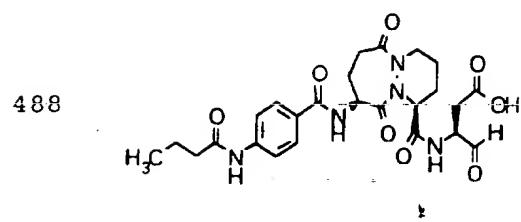
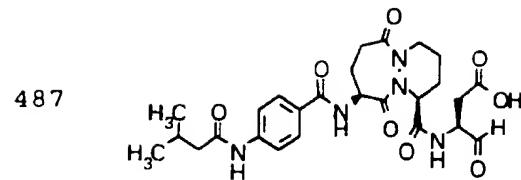


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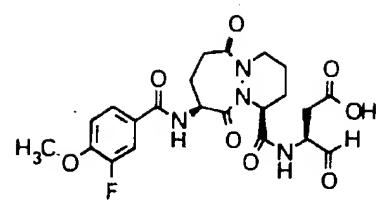


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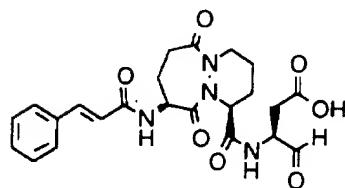


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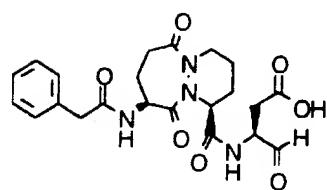
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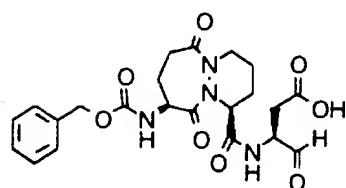
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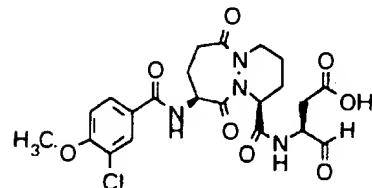


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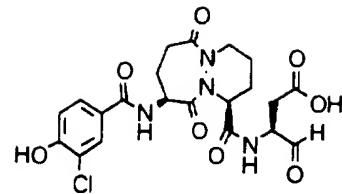
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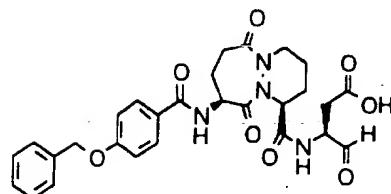


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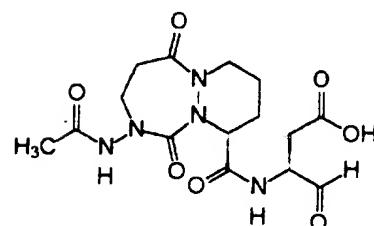
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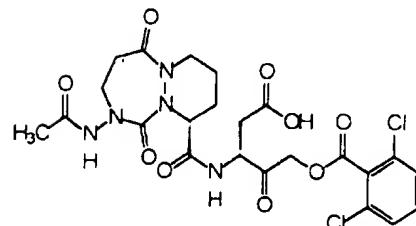
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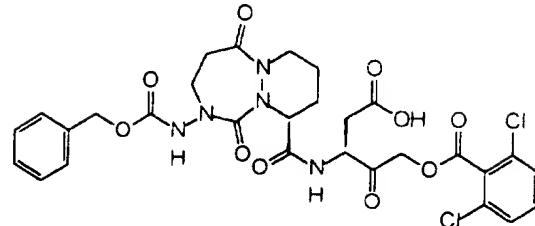


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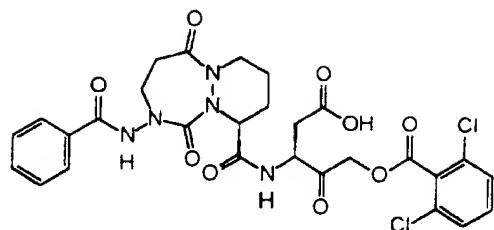
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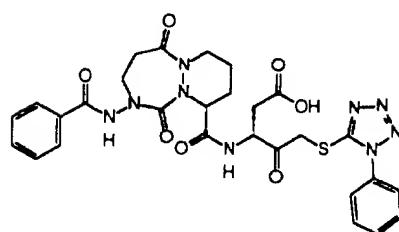


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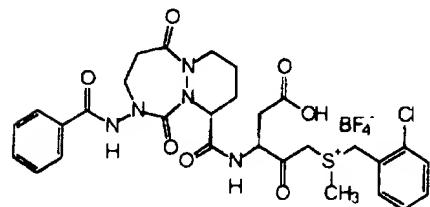
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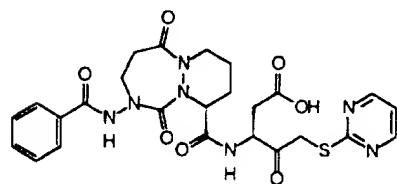
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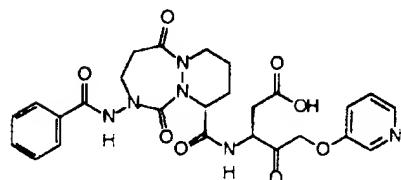


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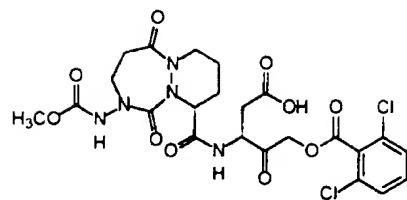
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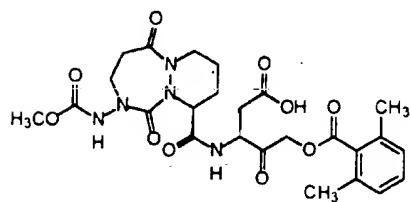


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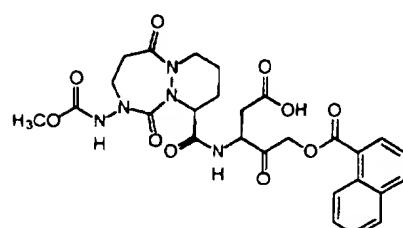
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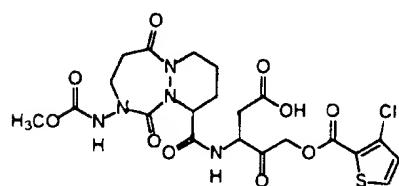
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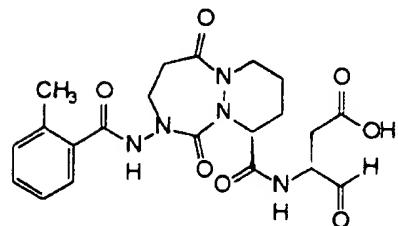


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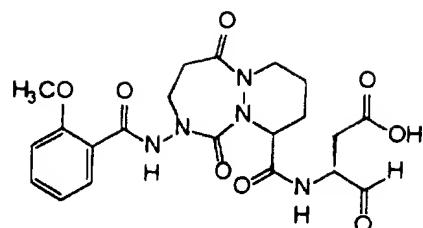
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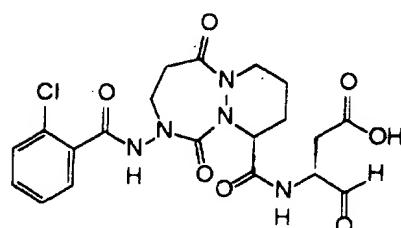


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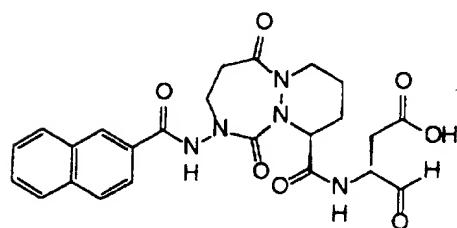
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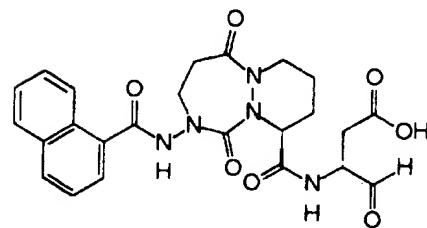
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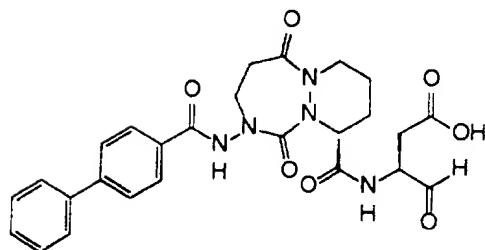


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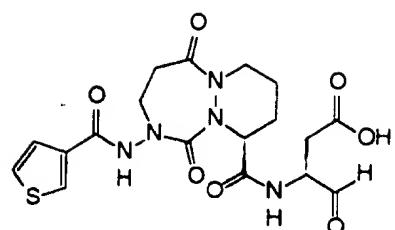
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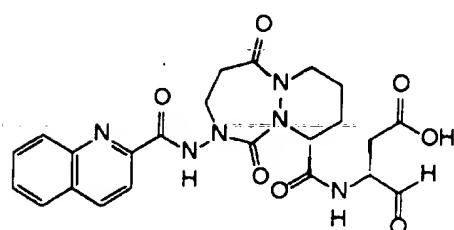


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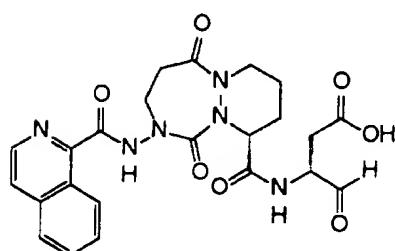
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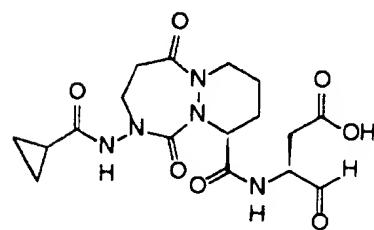
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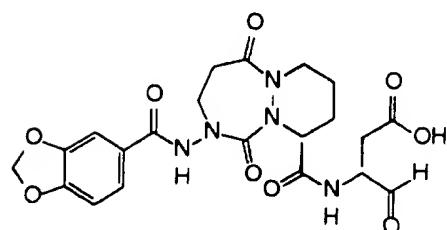


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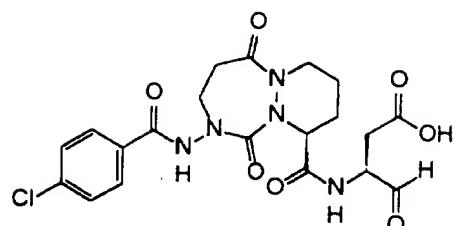
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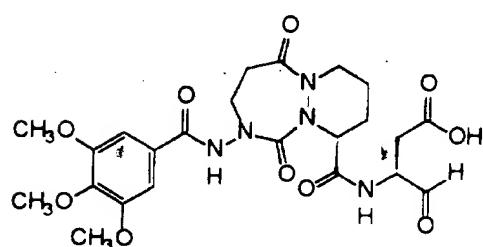


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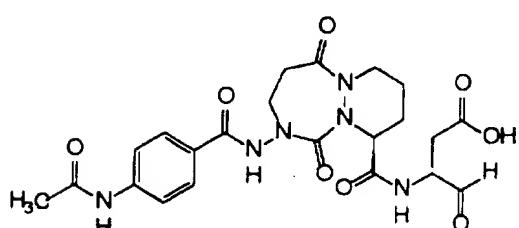
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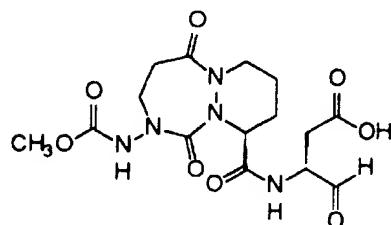
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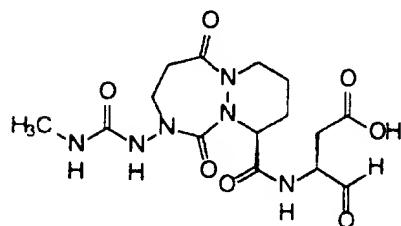


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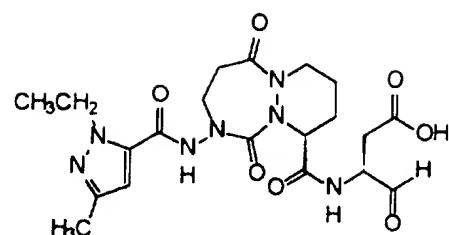
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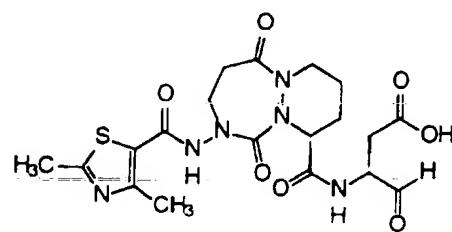


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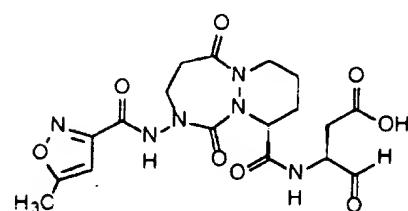
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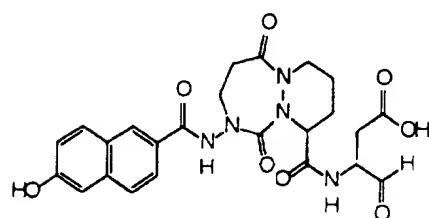
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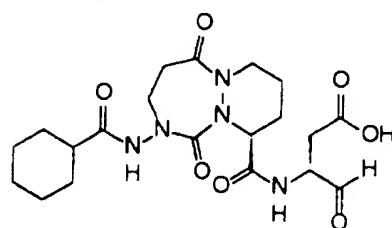


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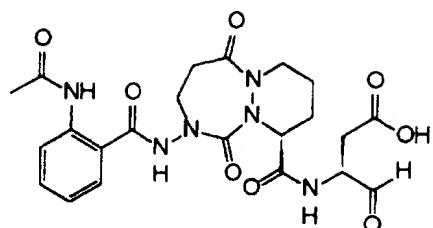
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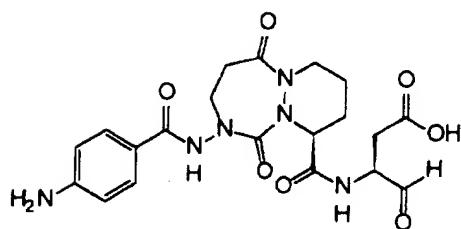


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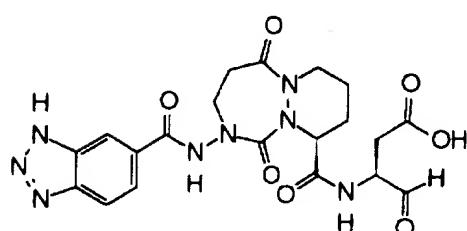
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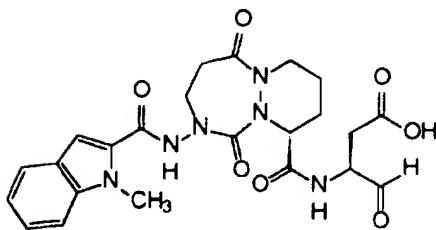
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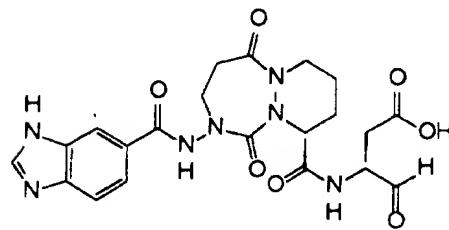


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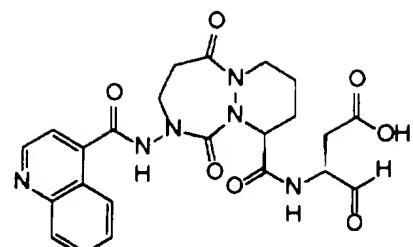
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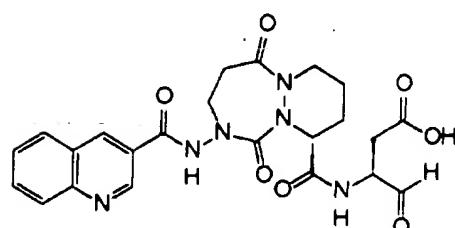


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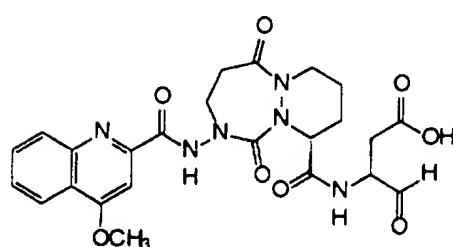
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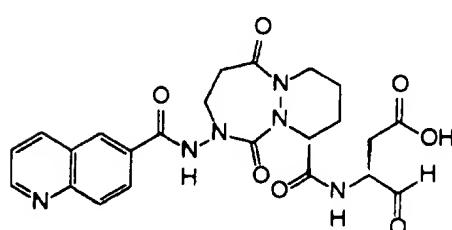
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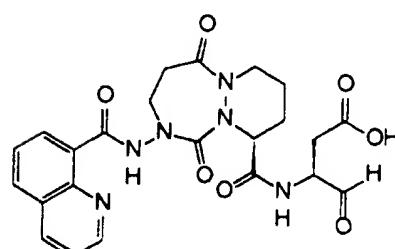


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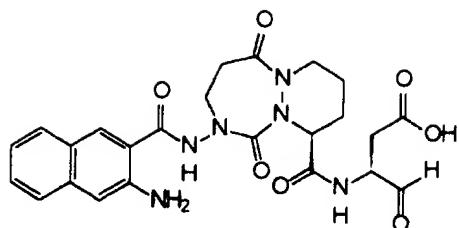
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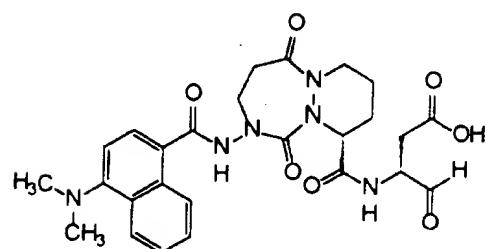


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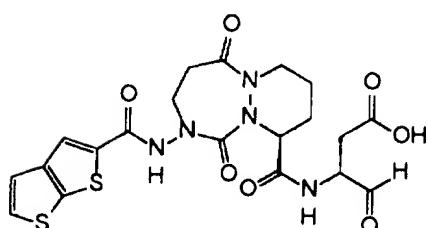
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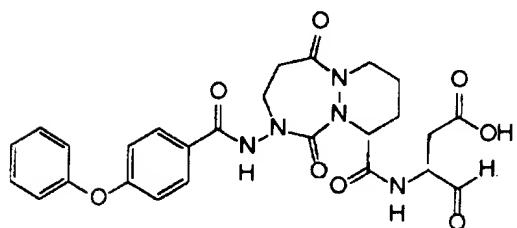
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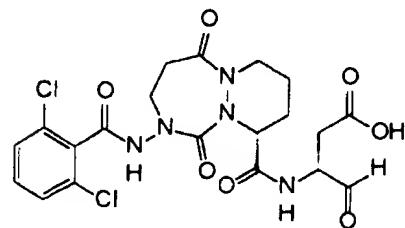


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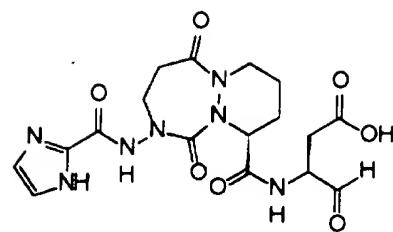
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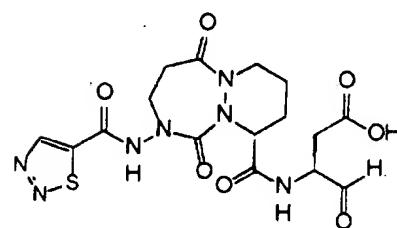


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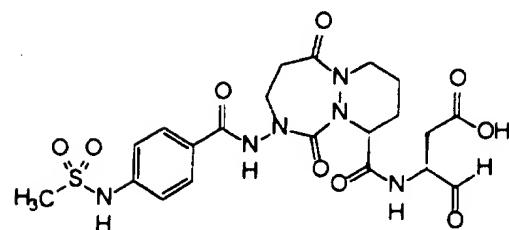
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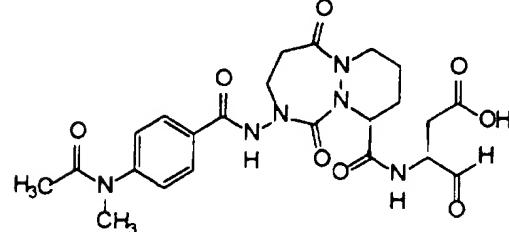
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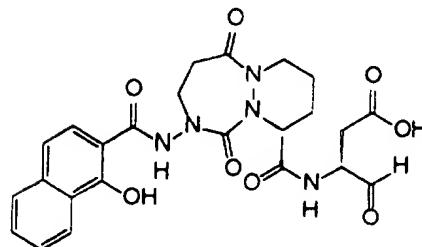


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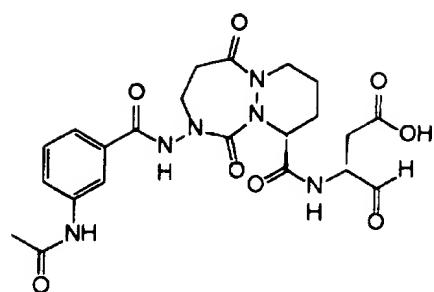
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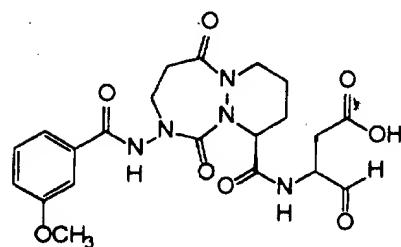


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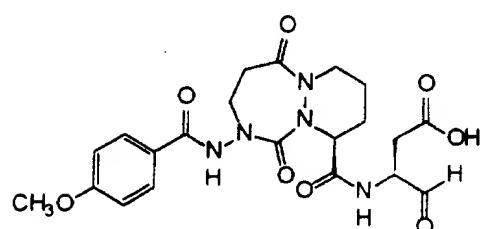
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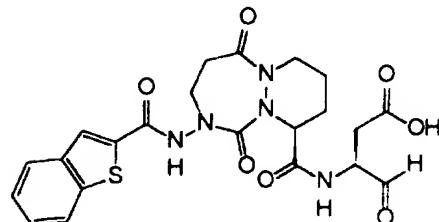
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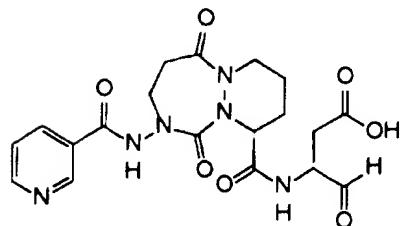


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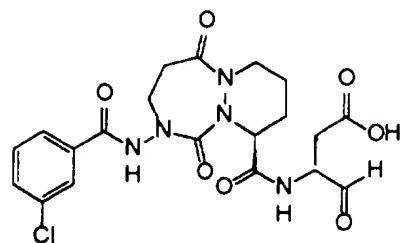
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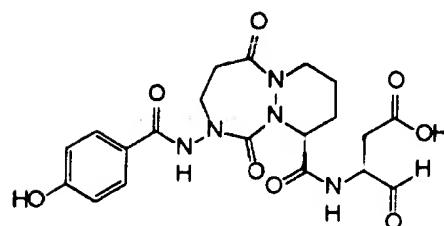


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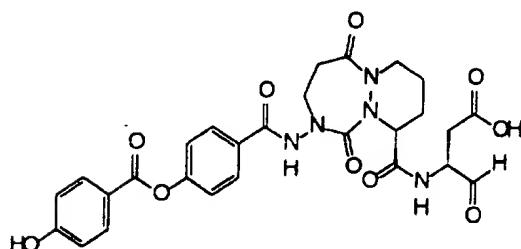
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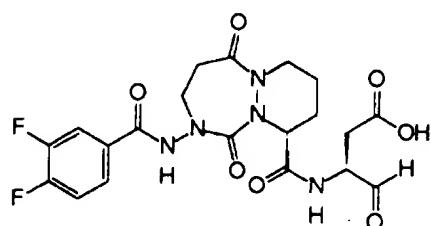
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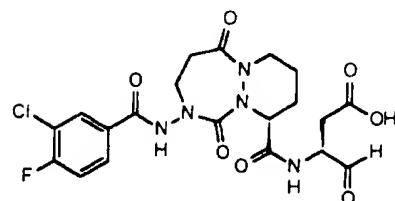


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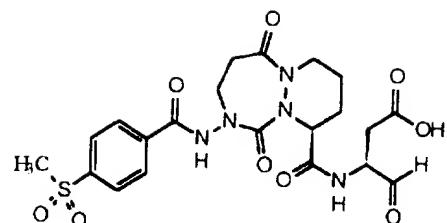
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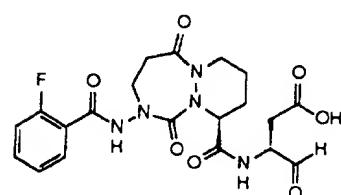


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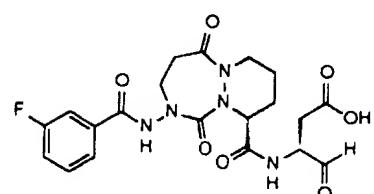
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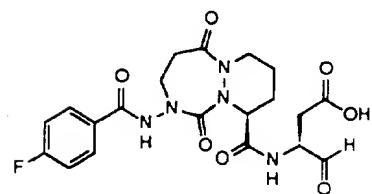
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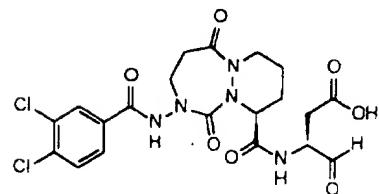


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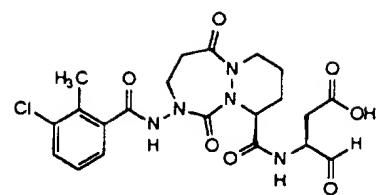
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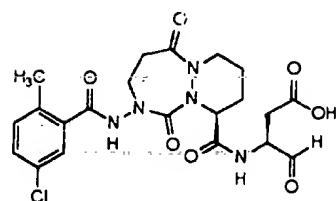


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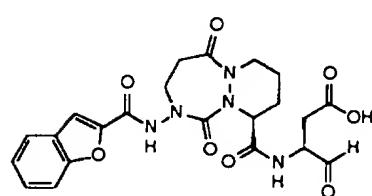
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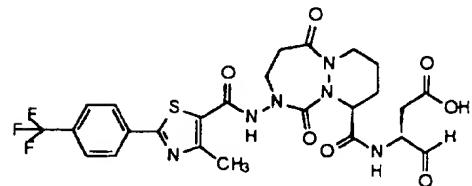
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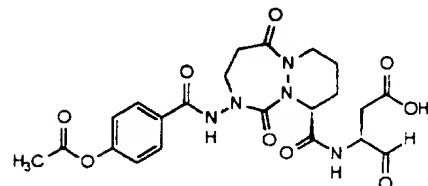


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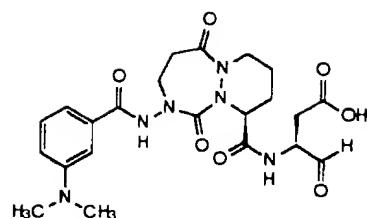
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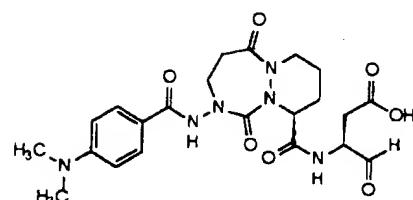


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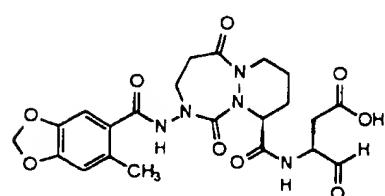
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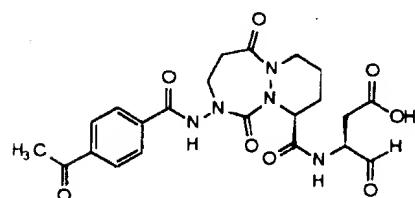
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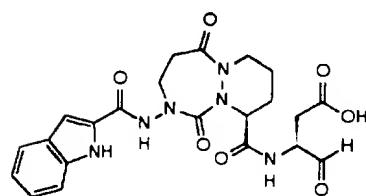


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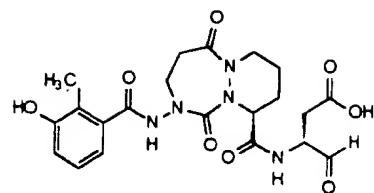
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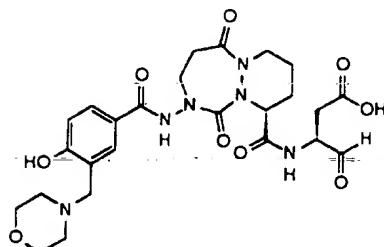


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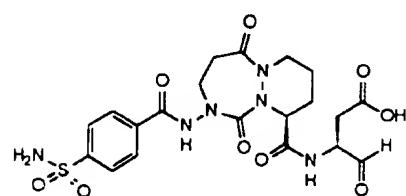
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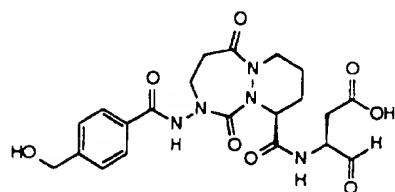
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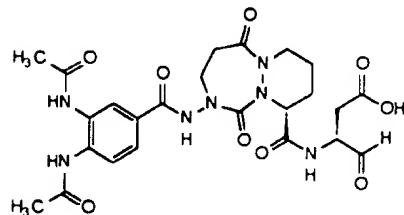


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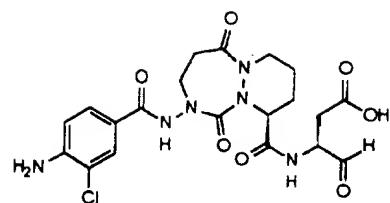
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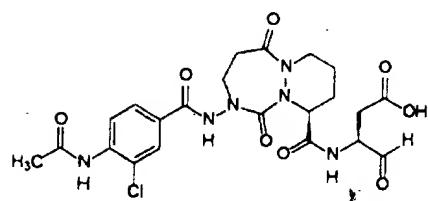


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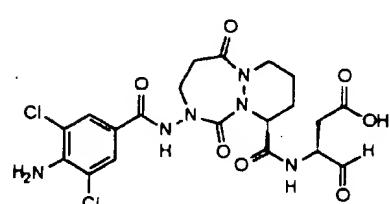
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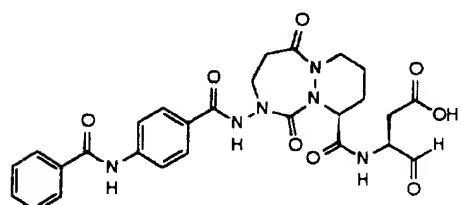
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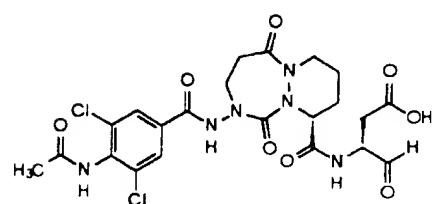


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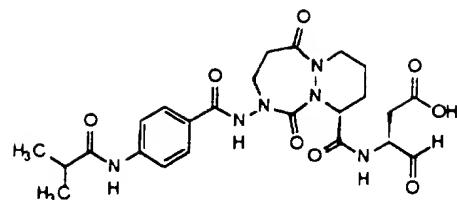
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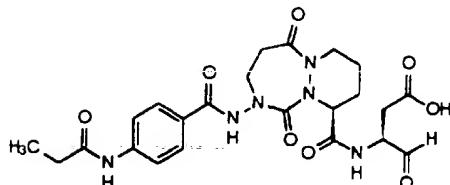


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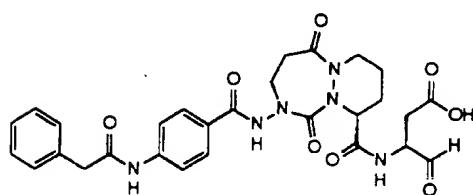
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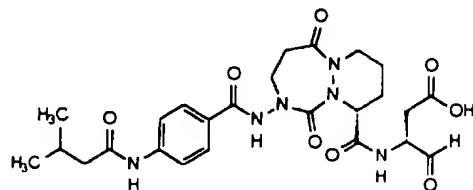
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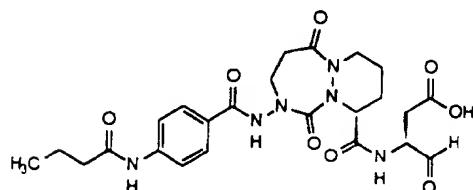


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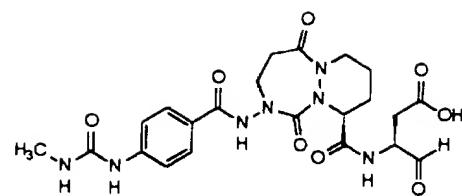
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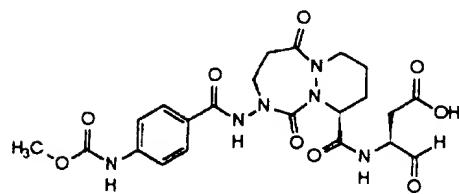


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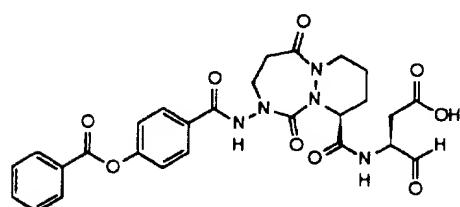
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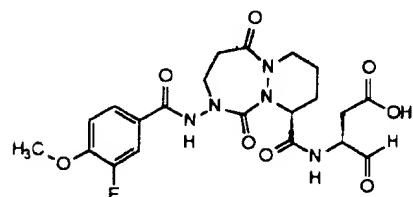
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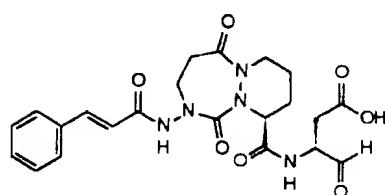


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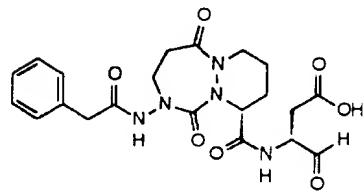


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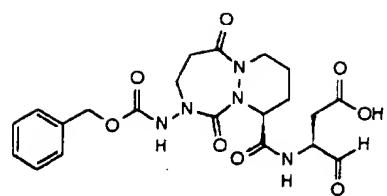


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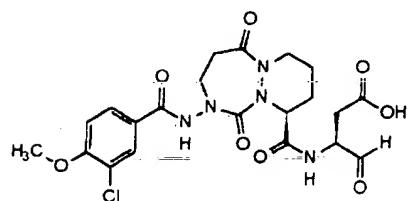


- 121 -

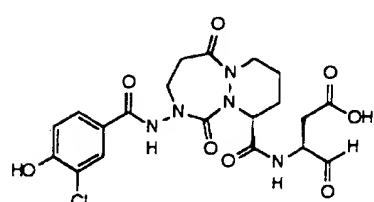
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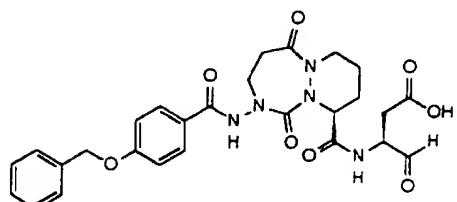
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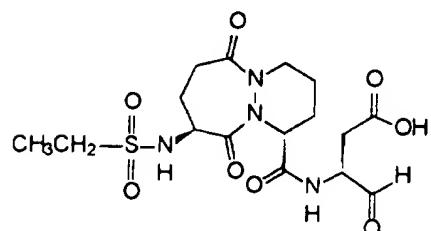


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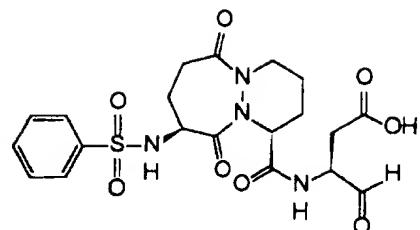
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421

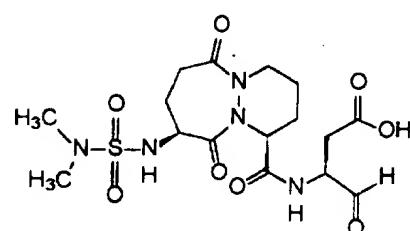


- 122 -

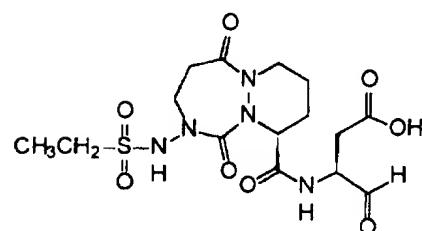
427



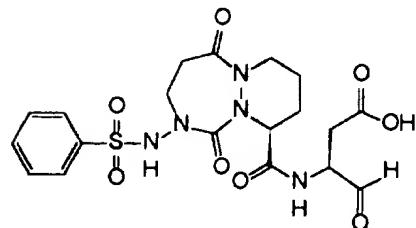
428



1021

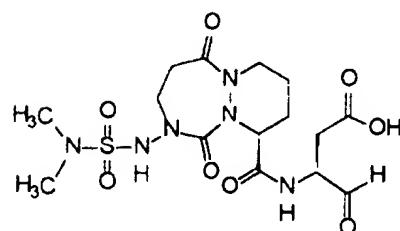


1027



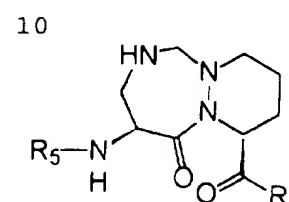
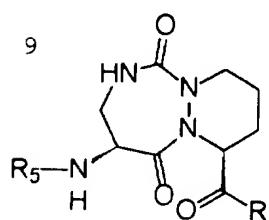
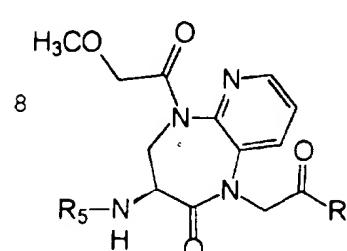
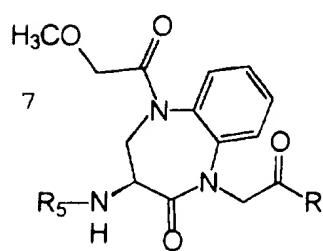
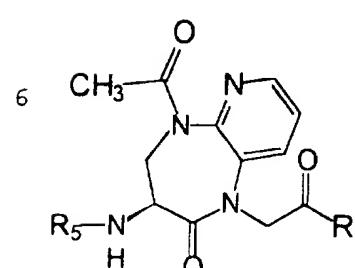
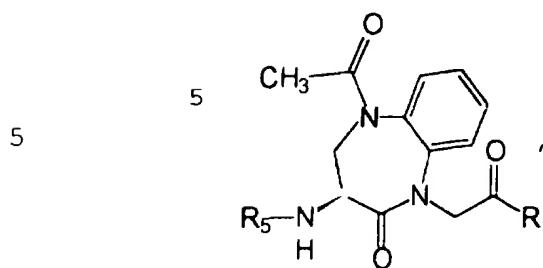
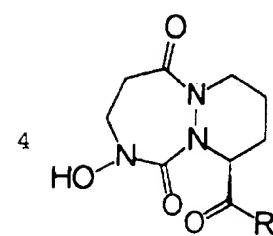
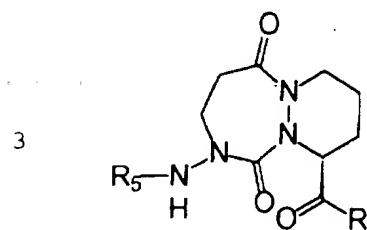
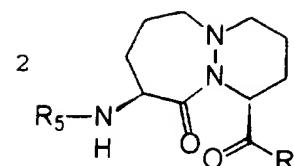
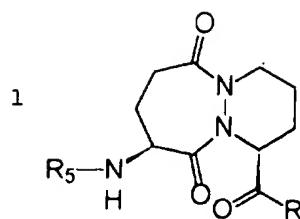
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1028

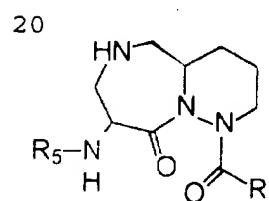
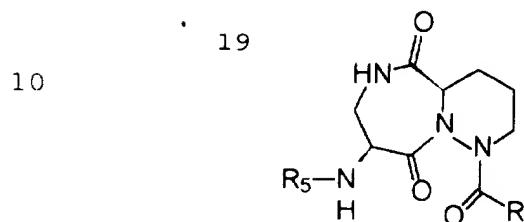
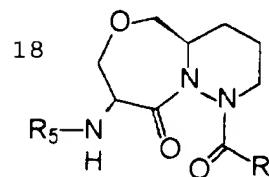
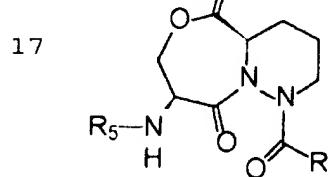
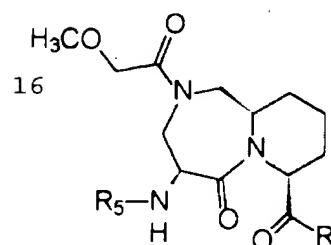
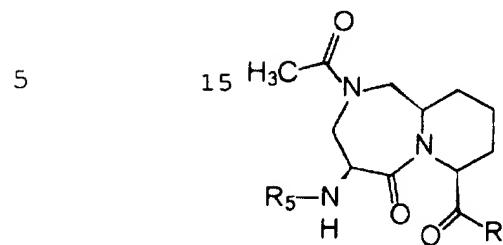
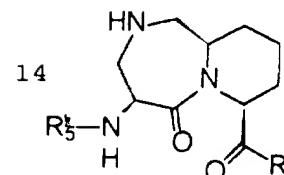
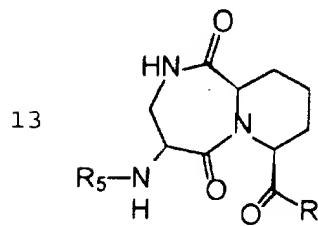
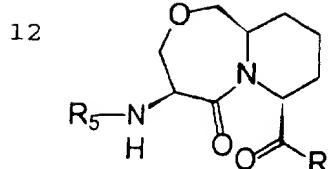
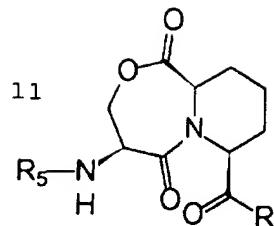


Specific compounds of this invention also include, but are not limited to, those compounds whose structures comprise scaffolds 1-22:

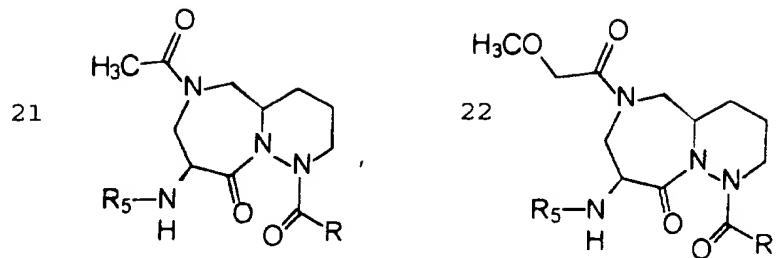
- 123 -



- 124 -



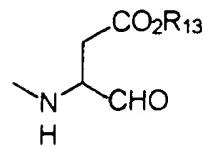
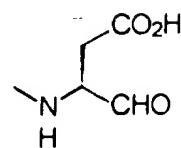
- 125 -



wherein:

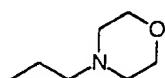
R is

5

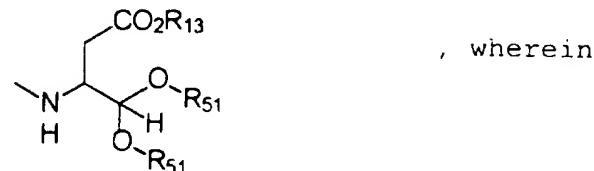


, wherein

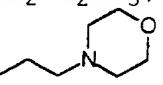
10



R_{13} is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)(CH_3)$,
 $-CH_2CH_2CH_2CH_3$, $-CH_2-CH(CH_3)CH_3$, $-C(CH_3)_3$, $-CH_2Ph$, or

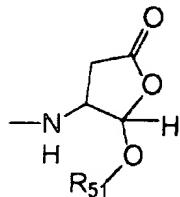


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R_{13} is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)(\text{CH}_3)$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{Ph}$,
or  , and

each R_{51} is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$,
5 $-\text{CH}(\text{CH}_3)(\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$,
 $-\text{CH}_2\text{Ph}$, or taken together form a ethylenedioxy acetal
or a propylenedioxy acetal; or

10



, wherein

R_{51} is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)(\text{CH}_3)$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{Ph}$,
 $-\text{C}(\text{O})-\text{CH}_3$ or $-\text{C}(\text{O})-\text{Ph}$;

15

R_5 in each of the above compounds is the same as
any one of the R_5 moieties shown for any one of
compounds 139, 214c, 214e, 404-413, 415-491, 493-501.

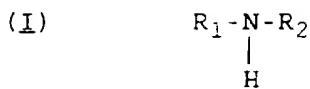
20

Specific compounds of this invention also include,
but are not limited to, compounds comprising scaffolds
1-28, wherein R , R_{51} , and R_5 are as defined above, and
in which the $-\text{C}(\text{O})-$ of the R_5 moiety of any one of
compounds 214c, 214e, 404-413, 415-418, 422-426, 430-
456, 458-466, 468, 470-471, 473-491, 493, 495, 497-501
is replaced with $-\text{CH}_2-$, $-\text{C}(\text{O})\text{C}(\text{O})-$, or $-\text{CH}_2\text{C}(\text{O})\text{C}(\text{O})-$.

25

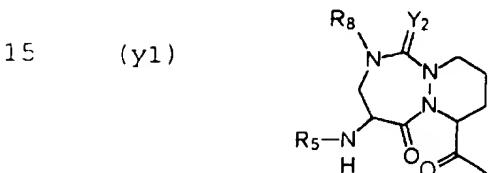
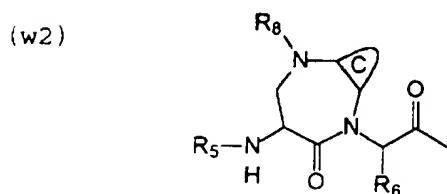
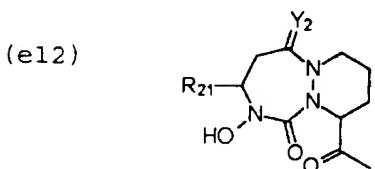
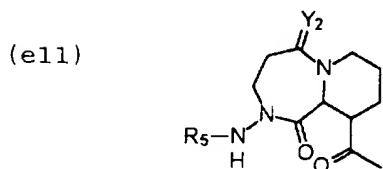
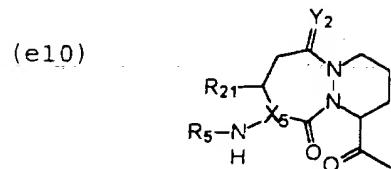
The ICE inhibitors of another embodiment (D)
of this invention are those of formula (I):

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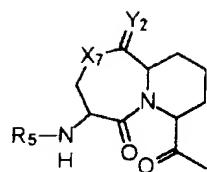
wherein:

5 R_1 is selected from the group consisting of the following formulae:



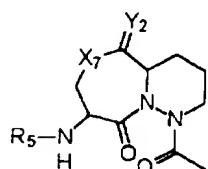
- 128 -

(y2)



;

(z)



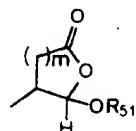
; and

ring C is chosen from the group consisting of
 5 benzo, pyrido, thieno, pyrrolo, furano, thiazolo,
 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,
 cyclopentyl, and cyclohexyl;

R₂ is:

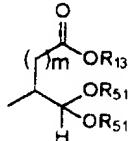
10

(a)



, or

(b)



;

m is 1 or 2;

each R₅ is independently selected from the group
 15 consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- S(O)₂-R₉,

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-S(O)₂-NH-R₁₀,
-C(O)-CH₂-O-R₉,
-C(O)C(O)-R₁₀,
-R₉,
5 -H,
-C(O)C(O)-OR₁₀, and
-C(O)C(O)-N(R₉)(R₁₀);

X₅ is -CH- or -N-;
10

Y₂ is H₂ or O;

X₇ is -N(R₈)- or -O-;

R₆ is selected from the group consisting of -H and
15 -CH₃;

R₈ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
20 -C(O)-N(H)-R₁₀,
-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-CH₂-OR₁₀,
-C(O)C(O)-R₁₀;
25 -C(O)-CH₂N(R₁₀)(R₁₀),
-C(O)-CH₂C(O)-O-R₉,
-C(O)-CH₂C(O)-R₉,
-H, and
-C(O)-C(O)-OR₁₀;

30 each R₉ is independently selected from the group
consisting of -Ar₃ and a -C₁₋₆ straight or branched
alkyl group optionally substituted with Ar₃, wherein

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the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

5 R_{13} is selected from the group consisting of H, Ar_3 , and a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3 , $-CQNH_2$, $-OR_5$, $-OH$,
10 $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9 , $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing $-O-$, $-S-$, or $-NH-$;

15 each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, and $-NH-$,
20 said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

25 each Q_1 is independently selected from the group
30

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consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, -N(R₉)(R₁₀), R₉, -C(O)-R₁₀, and



10 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

15 Preferably, R₅ is selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉, and
- C(O)-NH-R₁₀.

20 Alternatively, R₅ is selected from the group consisting of:

- S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-C(O)-R₁₀,
- R₉, and
- 25 -C(O)-C(O)-OR₁₀.

More preferably:

m is 1;

30 R₁₃ is H or a -C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

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R₂₁ is -H or -CH₃;

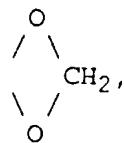
R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

5

each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

10 each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ where R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ where R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and

15 20

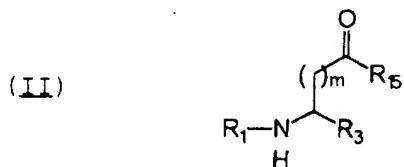


wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

25 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

30 The ICE inhibitors of another embodiment (E) of this invention are those of formula (II):

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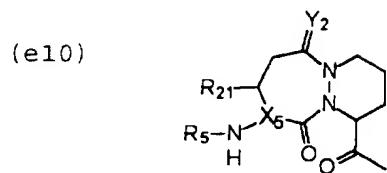


wherein:

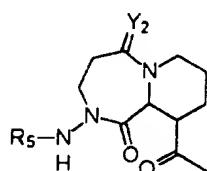
m is 1 or 2;

5

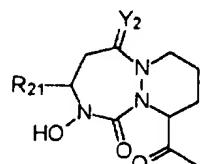
R_1 is selected from the group consisting of the following formulae:



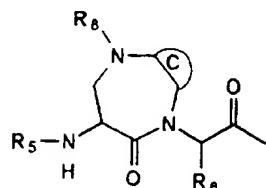
10 (e11)



(e12)

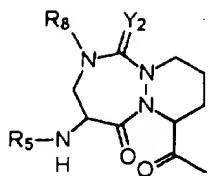


(w2)



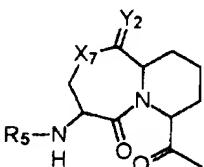
- 134 -

(y1)



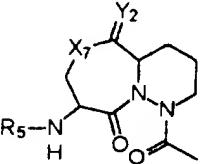
;

(y2)



;

(z)



; and

5

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

10 R₃ is selected from the group consisting of:
 -CN,
 -C(O)-H,
 -C(O)-CH₂-T₁-R₁₁,
 15 -C(O)-CH₂-F,
 -C=N-O-R₉, and
 -CO-Ar₂;

each R₅ is independently selected from the group consisting of:

20 -C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-N(R₁₀)(R₁₀)
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,

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-C(O)-CH₂-O-R₉,
-C(O)C(O)-R₁₀,
-R₉,
-H,
5 -C(O)C(O)-OR₁₀, and
-C(O)C(O)-N(R₉)(R₁₀);

X₅ is -CH- or -N-;
| |

10 Y₂ is H₂ or O;

X₇ is -N(R₈)- or -O-;

each T₁ is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

15 R₆ is selected from the group consisting of -H and -CH₃;

R₈ is selected from the group consisting of:

20 -C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-NH-R₁₀,
-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-CH₂-OR₁₀,
25 -C(O)C(O)-R₁₀,
-C(O)-CH₂-N(R₁₀)(R₁₀),
-C(O)-CH₂C(O)-O-R₉,
-C(O)-CH₂C(O)-R₉,
-H, and
30 -C(O)-C(O)-OR₁₀;

each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein

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the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of $-H$, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

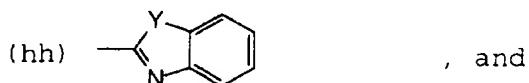
each R_{11} is independently selected from the group consisting of:

- 10 - Ar_4 ,
 - $(CH_2)_{1-3}-Ar_4$,
 - H , and
 - $C(O)-Ar_4$;

15 R_{15} is selected from the group consisting of $-OH$, $-OAr_3$, $-N(H)-OH$, and a $-OC_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

each R_{21} is independently selected from the group consisting of $-H$ or a $-C_{1-6}$ straight or branched alkyl group;

20 Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$:



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(ii)



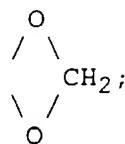
wherein each Y is independently selected from the group consisting of O and S;

5 each Ar₃ is a cyclic group independently selected
from the set consisting of an aryl group which contains
6, 10, 12, or 14 carbon atoms and between 1 and 3 rings
and an aromatic heterocycle group containing between 5
and 15 ring atoms and between 1 and 3 rings, said
10 heterocyclic group containing at least one heteroatom
group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
-N(R₅)-, and -N(R₉)- said heterocycle group optionally
containing one or more double bonds, said heterocycle
group optionally comprising one or more aromatic rings,
15 and said cyclic group optionally being singly or
multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected
from the set consisting of an aryl group which contains
6, 10, 12, or 14 carbon atoms and between 1 and 3
20 rings, and a heterocycle group containing between 5 and
15 ring atoms and between 1 and 3 rings, said
heterocyclic group containing at least one heteroatom
group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-,
-N(R₅)-, and -N(R₉)- said heterocycle group optionally
25 containing one or more double bonds, said heterocycle
group optionally comprising one or more aromatic rings,
and said cyclic group optionally being singly or
multiply substituted by -Q₁;

each Q₁ is independently selected from the group
30 consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN,
=O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉,
-N(R₉)(R₁₀), R₉, -C(O)-R₁₀, and

5



provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted 10 with another $-\text{Ar}_3$.

Preferred compounds of embodiment E employ formula (II), wherein R_1 is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment E 15 employ formula (II), wherein R_1 is (e12) and the other substituents are as defined above.

Other preferred compounds of embodiment E employ formula (II) wherein R_1 is (y1) and the other substituents are as defined above.

20 Other preferred compounds of embodiment E employ formula (II) wherein R_1 is (y2) and the other substituents are as defined above.

Other preferred compounds of embodiment E of 25 employ formula (II) wherein R_1 is (z) and the other substituents are as defined above.

Other preferred compound of embodiment E employ formula (II) wherein R_1 is (w2) and the other substituents are as defined above.

More preferably, R_1 is (w2) and

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m is 1;

ring C is benzo, pyrido, or thieno;

R₃ is selected from the group consisting of
-C(O)-H, -C(O)-Ar₂, and -C(O)CH₂-T₁-R₁₁;

5 R₅ is selected from the group consisting of:

-C(O)-R₁₀, wherein R₁₀ is -Ar₃;
-C(O)O-R₉, wherein R₉ is -CH₂-Ar₃;
-C(O)C(O)-R₁₀, wherein R₁₀ is -Ar₃;
-R₉, wherein R₉ is a C₁₋₂ alkyl group

10 substituted with -Ar₃; and

-C(O)C(O)-OR₁₀, wherein R₁₀ is -CH₂Ar₃;

T₁ is O or S;

R₆ is H;

15 R₈ is selected from the group consisting -C(O)-R₁₀,
-C(O)-CH₂-OR₁₀, and -C(O)CH₂-N(R₁₀)(R₁₀), wherein R₁₀ is
H, CH₃, or -CH₂CH₃;

R₁₁ is selected from the group consisting of -Ar₄,
-(CH₂)₁₋₃-Ar₄, and -C(O)-Ar₄;

20 R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl
group optionally substituted with -Ar₃, -OH, -OR₉, or
-CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight
alkyl group, wherein Ar₃ is morpholinyl or phenyl,
wherein the phenyl is optionally substituted with Q₁;

25 Ar₂ is (hh);

Y is O;

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each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl,
5 benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Ar₄ cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,
10 naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
15 wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;
25

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

30

Other preferred compounds of embodiment E employ formula (II) wherein R₁ is (e10), X₅ is CH, and the other substituents are as defined above.

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More preferred compounds of embodiment E employ formula (II) wherein R₁ is (e10), X₅ is CH, R₃ is CO-Ar₂, and the other substituents are as defined above.

5 Other more preferred compounds of embodiment E employ formula (II) wherein R₁ is (e10), X₅ is CH, R₃ is -C(O)-CH₂-T₁-R₁₁, R₁₁ is -(CH₂)₁₋₃-Ar₄, and the other substituents are as defined above.

10 Other more preferred compounds of embodiment E employ formula (II) wherein R₁ is (e10) and X₅ is CH and R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, R₁₁ is -C(O)-Ar₄, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

15 -C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

20 -S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉, and
-C(O)-C(O)-OR₁₀.

25 Most preferably, in these more preferred compounds,

m is 1;

T₁ is O or S;

R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl

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group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

5 R₂₁ is -H or -CH₃;

Ar₂ is (hh);

Y is O, and

each Ar₃ cyclic group is independently selected
10 from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,
15 and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Ar₄ cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,
20 said cyclic group being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
25 -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



wherein each R₉ and R₁₀ are independently a -C₁₋₆

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straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

Other more preferred compounds of embodiment E employ formula (II) wherein R₁ is (e10), X₅ is CH, R₃ is -C(O)-H, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

15 -C(O)-R₁₀,
 -C(O)O-R₉, and
 -C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

20 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-C(O)-R₁₀,
 -R₉, and
 -C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds,

25 m is 1;

R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, 30 wherein the phenyl is optionally substituted with Q₁;

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R₂₁ is -H or -CH₃;

each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thiienyl, 5 quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, said cyclic group optionally being singly or multiply substituted by -Q₁; 10

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



20 wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ 25 group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃,

Other more preferred compounds of embodiment E employ formula (II) wherein R₁ is (e10) and X₅ is CH, 30 R₃ is -CO-CH₂-T₁-R₁₁, and R₁₁ is -Ar₄, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

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-C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R₅ is
5 selected from the group consisting of:

-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉, and
10 -C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds,

m is 1;

T₁ is O or S;

15 R₁₅ is -OH or a -OC₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

20 R₂₁ is -H or -CH₃;

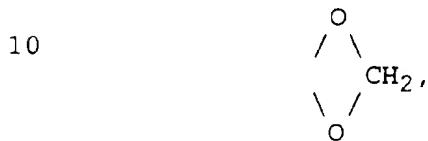
each Ar₃ cyclic group is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, 25 thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Ar₄ cyclic group is independently selected

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from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thiaryl, said cyclic group optionally being singly or multiply substituted by -Q₁;

5 each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

15 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

Other preferred compounds of embodiment E employ formula (II) wherein R₁ is (e10), X₅ is N, and the other substituents are as defined above.

25 More preferred compounds of embodiment E, employ formula (II) wherein R₁ is (e10), X₅ is N, R₃ is CO-Ar₂, and the other substituents are as defined above.

30 Other more preferred compounds of embodiment E, employ formula (II) wherein R₁ is (e10), X₅ is N, R₃ is -C(O)-CH₂-T₁-R₁₁, R₁₁ is -(CH₂)₁₋₃-Ar₄, and the other substituents are as defined above.

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Other more preferred compounds of embodiment E, employ formula (II) wherein R₁ is (e10) and X₅ is N and:

5 R₃ is -C(O)-CH₂-T₁-R₁₁;
 T₁ is O; and
 R₁₁ is -C(O)-Ar₄, and the other substituents are as defined above.

10 More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

15 Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉, and
20 -C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds, m is 1;

T₁ is O or S;

25 R₁₅ is -OH or a -OC₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

30 R₂₁ is -H or -CH₃;

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Ar₂ is (hh);

Y is O, and

each Ar₃ cyclic group is independently selected
5 from the set consisting of phenyl, naphthyl, thienyl,
quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,
isoxazolyl, benzotriazolyl, benzimidazolyl,
thienothienyl, imidazolyl, thiadiazolyl,
benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,
10 and said cyclic group optionally being singly or
multiply substituted by -Q₁;

each Ar₄ cyclic group is independently selected
from the set consisting of phenyl, tetrazolyl,
pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,
15 optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group
consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
-C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



25 wherein each R₉ and R₁₀ are independently a -C₁₋₆
straight or branched alkyl group optionally substituted
with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁
30 group which comprises one or more additional -Ar₃
groups, said additional -Ar₃ groups are not substituted
with another -Ar₃.

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Other more preferred compounds of embodiment E, employ formula (II) wherein R₁ is (e10), X₅ is N, R₃ is -C(O)-H, and the other substituents are as defined above.

5 More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉, and
- C(O)-NH-R₁₀.

10 Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

- S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-C(O)-R₁₀,
- 15 -R₉, and
- C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds,

m is 1;

20 R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

R₂₁ is -H or -CH₃;

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each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thiienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, 5 thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group 10 consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted 20 with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted 25 with another -Ar₃.

Other more preferred compounds of embodiment E, employ formula (II) wherein R₁ is (e10), X₅ is N, R₃ is -CO-CH₂-T₁-R₁₁, R₁₁ is -Ar₄, and the other substituents are as defined above.

30 More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉, and

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-C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

- 5 -S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉, and
-C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds

10 m is 1;

T₁ is O or S;

15 R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

R₂₁ is -H or -CH₃;

20 each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,
25 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

30 each Ar₄ cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl.

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said cyclic group being singly or multiply substituted by -Q₁;

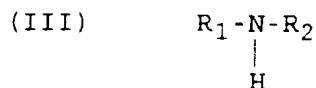
each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
 5 wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
 -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

15 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

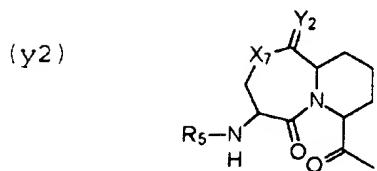
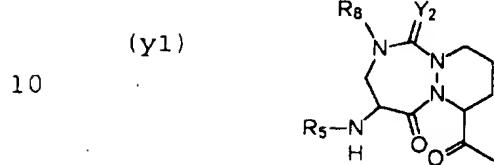
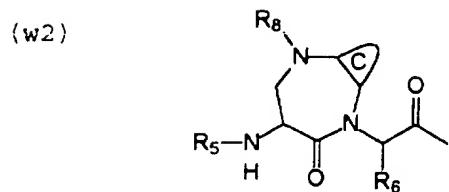
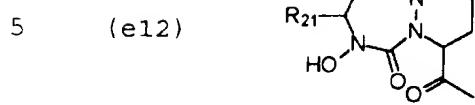
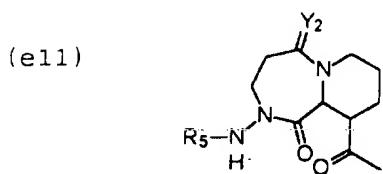
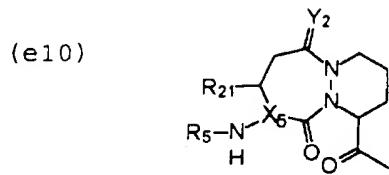
20 The ICE inhibitors of another embodiment (F) of this invention are those of formula (III):



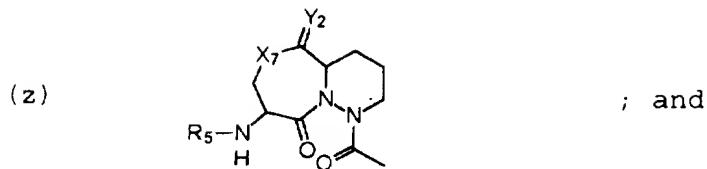
25 wherein:

R₁ is selected from the group consisting of the following formulae:

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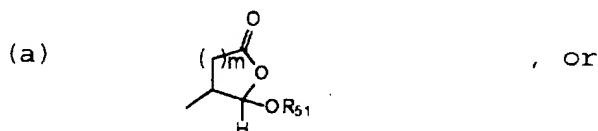


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ring C is chosen from the group consisting of
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,
5 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,
cyclopentyl, and cyclohexyl;

R₂ is:



m is 1 or 2;

each R₅ is independently selected from
the group consisting of:

- 15 -C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-CH₂-O-R₉,
- 20 -C(O)C(O)-R₁₀,
- R₉,
- H,

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-C(O)C(O)-OR₁₀, and
-C(O)C(O)-N(R₉)(R₁₀);

X₅ is CH or N;

5 Y₂ is H₂ or O;

X₇ is -N(R₈)- or -O-;

R₆ is selected from the group consisting of -H and
10 -CH₃;

R₈ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
15 -C(O)-N(H)-R₁₀,
-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-CH₂-OR₁₀,
-C(O)C(O)-R₁₀;
20 -C(O)-CH₂N(R₁₀)(R₁₀),
-C(O)-CH₂C(O)-O-R₉,
-C(O)-CH₂C(O)-R₉,
-H, and
-C(O)-C(O)-OR₁₀;

25 each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

each R₁₀ is independently selected from the group
30 consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is

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optionally unsaturated;

R₁₃ is selected from the group consisting of H, Ar₃, and a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, -CONH₂, -OR₅, -OH, 5 -OR₉, or -CO₂H;

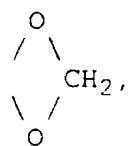
each R₂₁ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

each R₅₁ is independently selected from the group 10 consisting of R₉, -C(O)-R₉, -C(O)-N(H)-R₉, or each R₅₁ taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each Ar₃ is a cyclic group independently selected 15 from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-, 20 said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

25

each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, 30 -N(R₉)(R₁₀), R₉, -C(O)-R₁₀, and



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provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferred compounds of embodiment F employ formula (III), wherein R_1 is (w2) and the other substituents are as defined above.

10 Preferably, when R_1 is (w2):

m is 1;

ring C is benzo, pyrido, or thieno;

R_5 is selected from the group consisting of:

-C(O)- R_{10} , wherein R_{10} is $-Ar_3$;

15 -C(O)O- R_9 , wherein R_9 is $-CH_2-Ar_3$;

-C(O)C(O)- R_{10} , wherein R_{10} is $-Ar_3$;

- R_9 , wherein R_9 is a C_{1-2} alkyl group substituted with $-Ar_3$; and

-C(O)C(O)-OR $_{10}$, wherein R_{10} is $-CH_2Ar_3$;

20

R_6 is H;

R_8 is selected from the group consisting -C(O)- R_{10} , -C(O)- CH_2-OR_{10} , and -C(O) $CH_2-N(R_{10})(R_{10})$, wherein R_{10} is H, CH_3 , or $-CH_2CH_3$;

25

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with Ar_3 , -OH, -OR $_9$, -CO $_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

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Ar₃ is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, 5 benzo[b]thiophenyl, benzofuranyl, and indolyl;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and



15 wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ 20 group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

Other preferred compounds of embodiment F employ 25 formula (III), wherein R₁ is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R₁ is (e12) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ 30 formula (III), wherein R₁ is (y1) and the other substituents are as defined above.

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Other preferred compounds of embodiment F employ formula (III), wherein R₁ is (y₂) and the other substituents are as defined above.

5 Other preferred compounds of embodiment F employ formula (III), wherein R₁ is (z) and the other substituents are as defined above.

10 Other preferred compounds of embodiment F employ formula (III), wherein R₁ is (e₁₀) and X₅ is CH (also referred to herein as e₁₀-B), and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R₁ is (e₁₀) and X₅ is N, (also referred to herein as e₁₀-A) and the other substituents are as defined above.

15 Preferably, when R₁ is (e₁₁), (e₁₂), (y₁), (y₂), (z), (e₁₀-A), and (e₁₀-B), R₅ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉, and
20 -C(O)-NH-R₁₀.

Alternatively, when R₁ is (e₁₁), (e₁₂), (y₁), (y₂), (z), (e₁₀-A), and (e₁₀-B), R₅ is selected from the group consisting of:

25 -S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉,
-C(O)-C(O)-OR₁₀, and
-C(O)C(O)-N(R₉)(R₁₀).

30 More preferably, R₅ is R-C(O)-C(O)-R₁₀.

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Alternatively, R_5 is $-C(O)-C(O)-OR_{10}$.

More preferably when R_1 is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B):

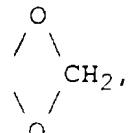
m is 1;

5 R_{21} is -H or -CH₃;

R_{51} is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar_3 , wherein the Ar_3 cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by -Q₁;

10 each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, 15 benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ 20 wherein R₅ is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, -OR₅ wherein R₅ is $-C(O)-R_{10}$, -OR₉, -N(R₉)(R₁₀), and



25

wherein each R₉ and R₁₀ are independently a C₁₋₆ straight or branched alkyl group optionally substituted with Ar_3 , wherein the Ar_3 cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

provided that when -Ar₃ is substituted with a -Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted 5 with another -Ar₃.

More preferably, in these more preferred compounds, the Ar₃ cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, 10 isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁.

15 Compounds in a preferred form of this embodiment F are those wherein:

R₅ is -C(O)-R₁₀, wherein:

20 R₁₀ is Ar₃, wherein the Ar₃ cyclic group is phenyl, said cyclic group optionally being singly or multiply substituted by:

-F,
-Cl,
-N(H)-R₅, wherein -R₅ is -H or -C(O)-R₁₀, wherein R₁₀ is a -C₁₋₆ straight or branched alkyl group 25 optionally substituted with Ar₃, wherein the Ar₃ cyclic group is phenyl, said cyclic group optionally being singly or multiply substituted by -Q₁,

-N(R₉)(R₁₀), wherein R₉ and R₁₀ are independently a -C₁₋₄ straight or branched alkyl group, or

30 -O-R₅, wherein R₅ is H or a -C₁₋₄ straight or branched alkyl group.

More preferably the Ar₃ cyclic group is phenyl optionally being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R₅, -N(R₉)(R₁₀), or -O-R₅.

5 Other preferred compounds of embodiment F include those wherein R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃ cyclic group is selected from the group consisting of indolyl, benzimidazolyl, thiienyl, and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

10 Other preferred compounds of embodiment F include those wherein R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃ cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁.

15 Other preferred compounds of embodiment F are those wherein R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃; wherein the Ar₃ cyclic group is phenyl, substituted by



25 In another form of embodiment F the compounds are as described above, further provided that when:

m is 1;
R₁ is (e10);
X₅ is CH;
R₁₅ is -OH;
30 R₂₁ is -H; and

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Y₂ is O and R₃ is -C(O)-H, then R₅ cannot be:
-C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic
group is phenyl, unsubstituted by -Q₁, 4-
(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-
5 (4-methylpiperazino)methylphenyl, or
-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃
cyclic group is phenyl, unsubstituted by -Q₁; and when

Y₂ is O, R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, and R₁₁
is Ar₄, wherein the Ar₄ cyclic group is 5-(1-(4-
10 chlorophenyl)-3-trifluoromethyl)pyrazolyl, then R₅
cannot be:

-C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic
group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-
(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl,
15 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-
fluorophenyl, 2-pyridyl, N-(4-
methylpiperazino)methylphenyl, or
-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃ and the Ar₃
cyclic group is phenyl;

20 and when R₁₁ is Ar₄, wherein the Ar₄ cyclic group
is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl, then R₅
cannot be:

-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃
cyclic group is phenyl;

25 and when R₁₁ is Ar₄, wherein the Ar₄ cyclic group
is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl, then
R₅ cannot be:

-C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic
group is 4-(dimethylaminomethyl)phenyl, or

30 -C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃
cyclic group is phenyl, unsubstituted by -Q₁; and when

Y₂ is O, R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, and R₁₁
is -C(O)-Ar₄, wherein the Ar₄ cyclic group is 2,5-

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dichlorophenyl, then R₅ cannot be:

-C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-

5 methyldipiperazino)methyl)phenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-carboethoxy-5-benzimidazolyl, or

10 -C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl, unsubstituted by -Q₁; and when

Y₂ is H₂, R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, and R₁₁ is

-C(O)-Ar₄, wherein the Ar₄ cyclic group is 2,5-dichlorophenyl, then R₅ cannot be:

15 -C(O)-OR₉, wherein R₉ is -CH₂-Ar₃ and the Ar₃ cyclic group is phenyl.

In another form of embodiment F, preferred compounds are those wherein R₂₁ is -H.

20 Alternatively, preferred compounds are those wherein R₂₁ is -CH₃.

Preferred compounds of embodiment F employ formula (III), wherein R₁ is (w2) and the other substituents are as defined above.

More preferably, R₁ is (w2) and

25 m is 1;

ring C is benzo, pyrido, or thieno;

R₃ is selected from the group consisting of -C(O)-H, -C(O)-Ar₂, and -C(O)CH₂-T₁-R₁₁;

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R₅ is selected from the group consisting of:

- C(O)-R₁₀, wherein R₁₀ is -Ar₃;
- C(O)O-R₉, wherein R₉ is -CH₂-Ar₃;
- C(O)C(O)-R₁₀, wherein R₁₀ is -Ar₃;
- 5 -R₉, wherein R₉ is a C₁₋₂ alkyl group substituted with -Ar₃; and
- C(O)C(O)-OR₁₀, wherein R₁₀ is -CH₂Ar₃;

T₁ is O or S;

10 R₆ is H;

R₈ is selected from the group consisting of -C(O)-R₁₀, -C(O)-CH₂-OR₁₀, and -C(O)CH₂-N(R₁₀)(R₁₀), wherein R₁₀ is H, CH₃, or -CH₂CH₃;

15 R₁₁ is selected from the group consisting of -Ar₄, -(CH₂)₁₋₃-Ar₄, and -C(O)-Ar₄;

R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl,
20 wherein the phenyl is optionally substituted with Q₁;

Ar₂ is (hh);

Y is O;

each Ar₃ cyclic group is independently selected
25 from the set consisting of phenyl, naphthyl, thiienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply
30 substituted by -Q₁;

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each Ar₄ cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



15 wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

20 Other preferred compounds of embodiment F employ formula (III), wherein R₁ is (e11) and the other
25 substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R₁ is (e12) and the other substituents are as defined above.

30 Other preferred compounds of embodiment F employ formula (III) wherein R₁ is (y1) and the other substituents are as defined above.

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Other preferred compounds of embodiment F employ formula (III) wherein R₁ is (y₂) and the other substituents are as defined above.

5 Other preferred compounds of embodiment F of employ formula (III) wherein R₁ is (z) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III) wherein R₁ is (e₁₀), X₅ is CH, and the other substituents are as defined above.

10 Other preferred compounds of embodiment F employ formula (III) wherein R₁ is (e₁₀), X₅ is N, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

15 -C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

20 -S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉,
-C(O)-C(O)-OR₁₀, and
25 -C(O)C(O)-N(R₉)(R₁₀).

Most preferably, in these more preferred compounds,

m is 1;

R₁₃ is H or a -C₁₋₄ straight or branched alkyl

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group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

5 R₂₁ is -H or -CH₃;

R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

10 each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thiienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,
15 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

20 each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

30

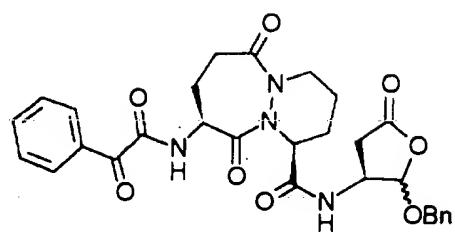
provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted

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with another -Ar_3 .

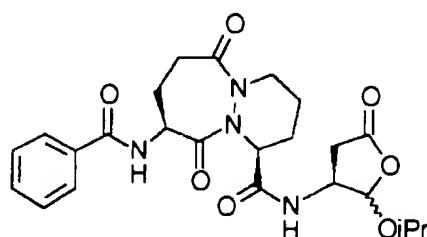
Preferred compounds of embodiment (F) include, but are not limited to:

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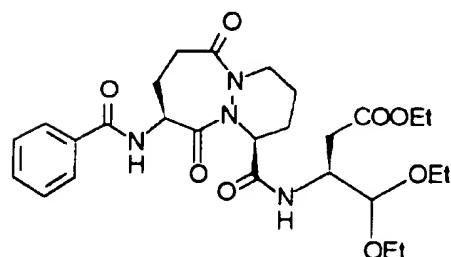


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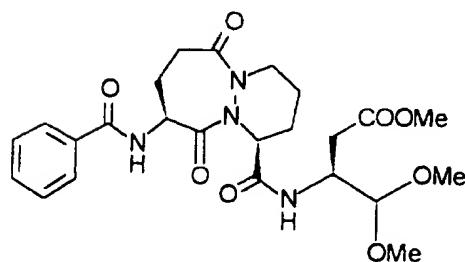
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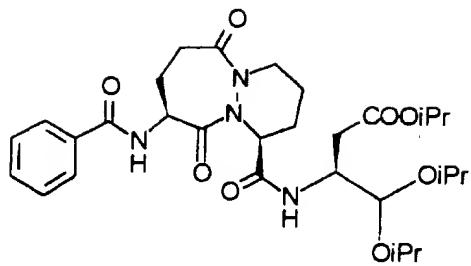


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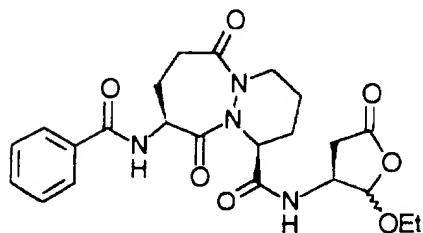


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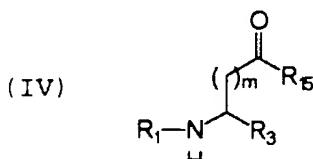
2100d



2100e



The ICE inhibitors of another embodiment (G)
5 of this invention are those of formula (IV) :

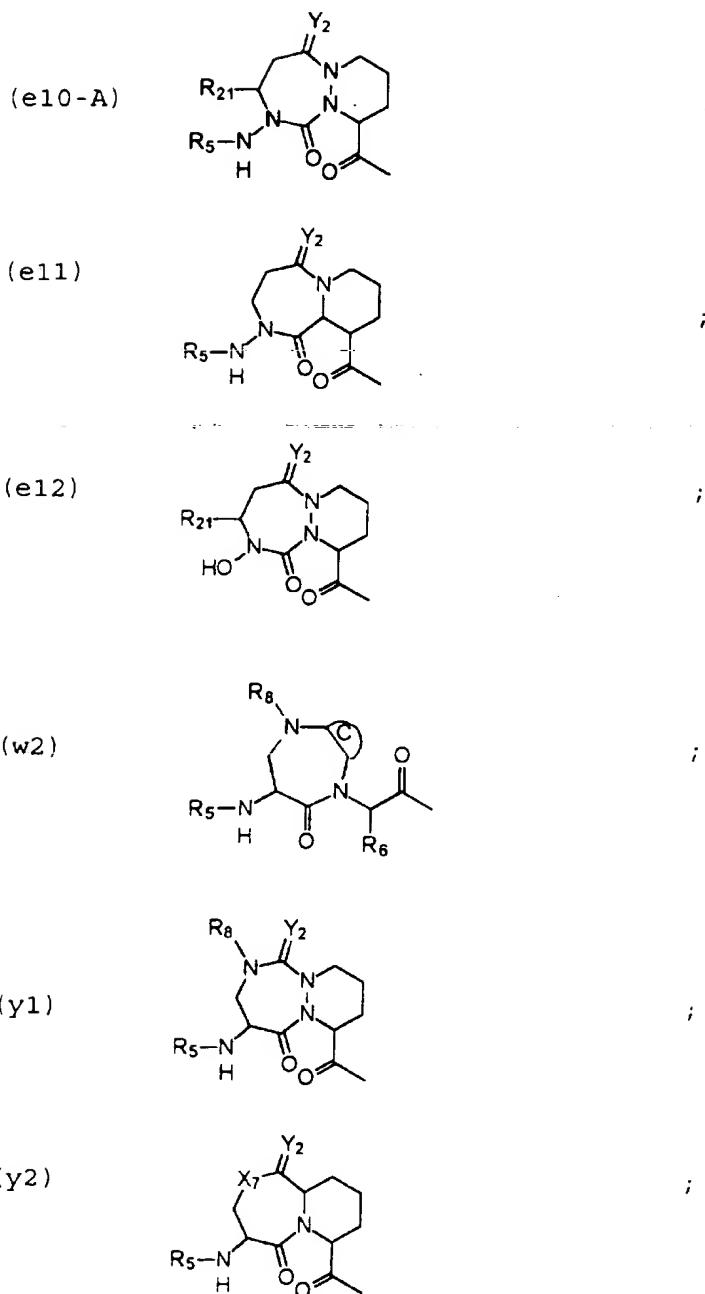


wherein:

m is 1 or 2;

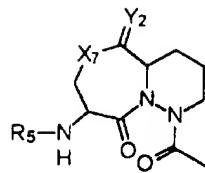
10 R₁ is selected from the group consisting of the following formulae:

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(z)



; and

ring C is chosen from the group consisting of
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,
5 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,
cyclopentyl, and cyclohexyl;

R₃ is selected from the group consisting of:

-CN,
-C(O)-H,
10 -C(O)-CH₂-T₁-R₁₁,
-C(O)-CH₂-F,
-C=N-O-R₉, and
-CO-Ar₂;

each R₅ is independently selected from the
15 group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-N(R₁₀)(R₁₀)
-S(O)₂-R₉,
20 -S(O)₂-NH-R₁₀,
-C(O)-CH₂-O-R₉,
-C(O)C(O)-R₁₀,
-R₉,
-H,
25 -C(O)C(O)-OR₁₀, and
-C(O)C(O)-N(R₉)(R₁₀);

Y₂ is H₂ or O;

X₇ is -N(R₈)- or -O-;

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each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2$;

5 R_6 is selected from the group consisting of -H and -CH₃;

R_8 is selected from the group consisting of:

10 -C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-NH-R₁₀,
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀,
15 -C(O)-CH₂-N(R₁₀)(R₁₀),
 -C(O)-CH₂C(O)-O-R₉,
 -C(O)-CH₂C(O)-R₉,
 -H, and
 -C(O)-C(O)-OR₁₀;

20 each R_9 is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

25 each R_{10} is independently selected from the group consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

30 each R_{11} is independently selected from the group consisting of:

-Ar₄,
- (CH₂)₁₋₃-Ar₄,
-H, and

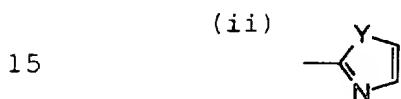
- 174 -

$-\text{C}(\text{O})-\text{Ar}_4;$

R_{15} is selected from the group consisting of $-\text{OH}$,
 $-\text{OAr}_3$, $-\text{N}(\text{H})-\text{OH}$, and $-\text{OC}_{1-6}$, wherein C_{1-6} is a straight
or branched alkyl group optionally substituted with
5 Ar_3 , $-\text{CONH}_2$, $-\text{OR}_5$, $-\text{OH}$, $-\text{OR}_9$, or $-\text{CO}_2\text{H}$;

each R_{21} is independently selected from the group
consisting of $-\text{H}$ or a $-\text{C}_{1-6}$ straight or branched alkyl
group;

10 Ar_2 is independently selected from the following
group, in which any ring may optionally be singly or
multiply substituted by $-\text{Q}_1$ or phenyl, optionally
substituted by Q_1 :



wherein each Y is independently selected from the
group consisting of O and S ;

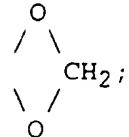
each Ar_3 is a cyclic group independently selected
from the set consisting of an aryl group which contains
20 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings
and an aromatic heterocycle group containing between 5
and 15 ring atoms and between 1 and 3 rings, said
heterocyclic group containing at least one heteroatom
group selected from $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, SO_2 , $=\text{N}-$, and $-\text{NH}-$,
25 $-\text{N}(\text{R}_5)-$, and $-\text{N}(\text{R}_9)-$ said heterocycle group optionally
containing one or more double bonds, said heterocycle
group optionally comprising one or more aromatic rings,
and said cyclic group optionally being singly or

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multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, -N(R₉)(R₁₀), R₉, -C(O)-R₁₀, and



20

25

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃;

Preferred compounds of embodiment G employ formula (IV), wherein R₁ is (w2) and the other substituents are as defined above.

Preferably, when R₁ is (w2):

30

m is 1;

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ring C is benzo, pyrido, or thieno;

R₅ is selected from the group consisting of:

- C(O)-R₁₀, wherein R₁₀ is -Ar₃;
- C(O)O-R₉, wherein R₉ is -CH₂-Ar₃;
- 5 -C(O)C(O)-R₁₀, wherein R₁₀ is -Ar₃;
- R₉, wherein R₉ is a C₁₋₂ alkyl group substituted with -Ar₃; and
- C(O)C(O)-OR₁₀, wherein R₁₀ is -CH₂Ar₃;

10 R₆ is H;

R₈ is selected from the group consisting -C(O)-R₁₀, -C(O)-CH₂-OR₁₀, and -C(O)CH₂-N(R₁₀)(R₁₀), wherein R₁₀ is H, CH₃, or -CH₂CH₃;

15 R₁₃ is H or a C₁₋₄ straight or branched alkyl group optionally substituted with Ar₃, -OH, -OR₉, -CO₂H, wherein the R₉ is a C₁₋₄ branched or straight chain alkyl group; wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

20 Ar₃ is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl;

25 each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and,



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wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

5 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

10 Other preferred compounds of embodiment G employ formula (IV) wherein R₁ is (e10-A) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein R₁ is (e11) and the other substituents are as defined above.

15 Other preferred compounds of embodiment G employ formula (IV) wherein R₁ is (e12) and the other substituents are as defined above.

20 Other preferred compounds of embodiment G employ formula (IV) wherein R₁ is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein R₁ is (y2) and the other substituents are as defined above.

25 Other preferred compounds of embodiment G employ formula (IV) wherein R₁ is (z) and the other substituents are as defined above.

More preferred compounds of embodiment G are those wherein R₃ is -CO-Ar₂.

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Most preferably, when R_3 is $-CO-Ar_2$, Y is O .

Other more preferred compounds are those wherein
 R_3 is $-C(O)-CH_2-T_1-R_{11}$ and R_{11} is $-(CH_2)_{1-3}-Ar_4$.

5 Most preferably, when R_3 is $-C(O)-CH_2-T_1-R_{11}$
and R_{11} is $-(CH_2)_{1-3}-Ar_4$, T_1 is O .

Other more preferred compounds are those wherein:
 R_3 is $-C(O)-CH_2-T_1-R_{11}$;
 T_1 is O ; and
 R_{11} is $-C(O)-Ar_4$.

10 Other more preferred compounds are those wherein
 R_3 is $-C(O)-H$.

Other more preferred compounds are those wherein
 R_3 is $-CO-CH_2-T_1-R_{11}$ and R_{11} is $-Ar_4$.

15 More preferably, when R_3 is $-CO-CH_2-T_1-R_{11}$ and
 R_{11} is $-Ar_4$, T_1 is O or S .

More preferably, when R_1 is $(e11)$, $(e12)$, $(y1)$,
 $(y2)$, (z) , $(e10-A)$, and $(e10-B)$, R_5 is selected from
the group consisting of:

20 $-C(O)-R_{10}$,
 $-C(O)O-R_9$, and
 $-C(O)-NH-R_{10}$.

Alternatively, when R_1 is $(e11)$, $(e12)$, $(y1)$,
 $(y2)$, (z) , $(e10-A)$, and $(e10-B)$, R_5 is selected from
the group consisting of:

25 $-S(O)_2-R_9$,
 $-S(O)_2-NH-R_{10}$,
 $-C(O)-C(O)-R_{10}$,
 $-R_9$,

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$-C(O)-C(O)-OR_{10}$, and
 $-C(O)-C(O)-N(R_9)(R_{10})$.

More preferably, R_5 is $-C(O)-C(O)-R_{10}$.

Alternatively, R_5 is $-C(O)-C(O)-OR_{10}$.

5 Most preferably, when R_1 is (e11), (e12), (y1), (y2),
(z), (e10-A), and (e10-B),:

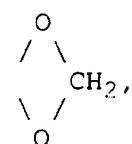
m is 1;

R_{21} is -H or -CH₃;

10 R_{51} is a C₁₋₆ straight or branched alkyl group
optionally substituted with Ar_3 , wherein the Ar_3 cyclic
group is phenyl, said cyclic group optionally being
multiply or singly substituted by -Q₁;

15 each Ar_3 cyclic group is independently selected
from the set consisting of phenyl, naphthyl, thiienyl,
quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,
isoxazolyl, benzotriazolyl, benzimidazolyl,
thienothienyl, imidazolyl, thiadiazolyl,
benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl,
and said cyclic group optionally being singly or
20 multiply substituted by -Q₁;

each Q₁ is independently selected from the group
consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
wherein R₅ is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, -OR₅ wherein R₅ is
25 $-C(O)-R_{10}$, -OR₉, -N(R₉)(R₁₀), and



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wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the Ar₃ cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

provided that when -Ar₃ is substituted with a -Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

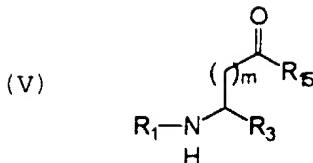
More preferably, in these more preferred compounds, the Ar₃ cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁.

Compounds in a preferred form of embodiment G are those wherein R₂₁ is H and the other substituents are as defined above.

Compounds in another preferred form of embodiment G are those wherein R₂₁ is CH₃ and the other substituents are as defined above.

The ICE inhibitors of another embodiment (H) of this invention are those of formula (V):

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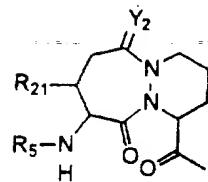


wherein:

m is 1 or 2;

5 R₁ is:

(e10-B)



;

R₃ is selected from the group consisting of:

- CN,
- C(O)-H,
- 10 -C(O)-CH₂-T₁-R₁₁,
- C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

each R₅ is independently selected from the group
15 consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- S(O)₂-R₉,
- 20 -S(O)₂-NH-R₁₀,
- C(O)-CH₂-O-R₉,
- C(O)C(O)-R₁₀,
- R₉,
- H, and
- 25 -C(O)C(O)-N(R₉)(R₁₀), and
- C(O)C(O)-OR₁₀;

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Y_2 is H₂ or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

5 R_8 is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-NH-R₁₀,
-S(O)₂-R₉,
10 -S(O)₂-NH-R₁₀,
-C(O)-CH₂-OR₁₀,
-C(O)C(O)-R₁₀,
-C(O)-CH₂-N(R₁₀)(R₁₀),
-C(O)-CH₂C(O)-O-R₉,
15 -C(O)-CH₂C(O)-R₉,
-H, and
-C(O)-C(O)-OR₁₀;

each R_9 is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

20 each R_{10} is independently selected from the group consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

25 -Ar₄,
- (CH₂)₁₋₃-Ar₄,
-H, and
-C(O)-Ar₄;

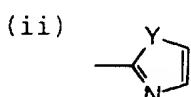
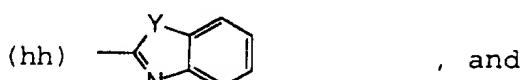
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R_{15} is selected from the group consisting of $-OH$, $-OAr_3$, $-N(H)-OH$, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with Ar_3 ,

5 $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

R_{21} is $-CH_3$;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally
10 substituted by Q_1 :



wherein each Y is independently selected from the
15 group consisting of O and S;

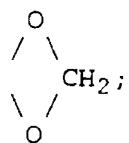
each Ar_3 is a cyclic group independently selected
from the set consisting of an aryl group which contains
6, 10, 12, or 14 carbon atoms and between 1 and 3 rings
and an aromatic heterocycle group containing between 5
20 and 15 ring atoms and between 1 and 3 rings, said
heterocyclic group containing at least one heteroatom
group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, and $-NH-$,
 $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally
containing one or more double bonds, said heterocycle
group optionally comprising one or more aromatic rings,
25 and said cyclic group optionally being singly or
multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected

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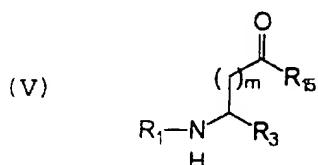
from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said 5 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, 10 and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, 15 -N(R₉)(R₁₀), R₉, -C(O)-R₁₀, and



20 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃;

25 Compounds of another form of embodiment (I) (form 1) are those of formula (V):

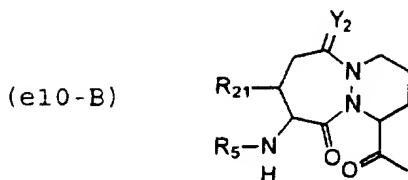


wherein:

m is 1 or 2;

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R₁ is:



R₃ is selected from the group consisting of:

- CN,
- 5 -C(O)-H,
- C(O)-CH₂-T₁-R₁₁,
- C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

10 each R₅ is -C(O)C(O)-OR₁₀;

Y₂ is H₂ or O;

each T₁ is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

15

R₈ is selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-NH-R₁₀,
- 20 -S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-CH₂-OR₁₀,
- C(O)C(O)-R₁₀,
- C(O)-CH₂-N(R₁₀)(R₁₀),
- 25 -C(O)-CH₂C(O)-O-R₉,
- C(O)-CH₂C(O)-R₉,
- H, and
- C(O)-C(O)-OR₁₀;

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each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

5 each R₁₀ is independently selected from the group consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

10 each R₁₁ is independently selected from the group consisting of:

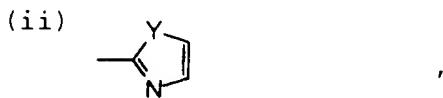
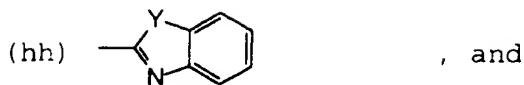
-Ar₄,
-(CH₂)₁₋₃-Ar₄,
-H, and
15 -C(O)-Ar₄;

R₁₅ is selected from the group consisting of -OH, -OAr₃, -N(H)-OH, and -OC₁₋₆, wherein C₁₋₆ is a straight or branched alkyl group optionally substituted with Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

20 each R₂₁ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

Ar₂ is independently selected from the following group, in which any ring may optionally be singly or 25 multiply substituted by -Q₁ or phenyl, optionally substituted by Q₁:

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wherein each Y is independently selected from the
5 group consisting of O and S;

each Ar₃ is a cyclic group independently selected
from the set consisting of an aryl group which contains
6, 10, 12, or 14 carbon atoms and between 1 and 3 rings
and an aromatic heterocycle group containing between 5
10 and 15 ring atoms and between 1 and 3 rings, said
heterocyclic group containing at least one heteroatom
group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
-N(R₅)-, and -N(R₉)- said heterocycle group optionally
containing one or more double bonds, said heterocycle
15 group optionally comprising one or more aromatic rings,
and said cyclic group optionally being singly or
multiply substituted by -Q₁;

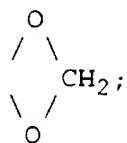
each Ar₄ is a cyclic group independently selected
from the set consisting of an aryl group which contains
20 6, 10, 12, or 14 carbon atoms and between 1 and 3
rings, and a heterocycle group containing between 5 and
15 ring atoms and between 1 and 3 rings, said
heterocyclic group containing at least one heteroatom
group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-,
-N(R₅)-, and -N(R₉)- said heterocycle group optionally
25 containing one or more double bonds, said heterocycle
group optionally comprising one or more aromatic rings,
and said cyclic group optionally being singly or
multiply substituted by -Q₁;

30 each Q₁ is independently selected from the group

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consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, -N(R₉)(R₁₀), R₉, -C(O)-R₁₀, and

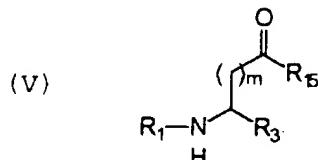
5



provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃;

Alternatively, compounds of this form of embodiment I (form 2) are those wherein R₂₁ is -CH₃.

15 Compounds of another form of embodiment (J) (form 1) are those of formula (V):

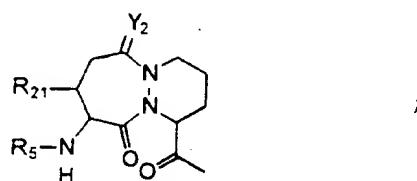


wherein:

m is 1 or 2;

20 R₁ is:

(e10-B)



R₃ is selected from the group consisting of:

- CN,
- C(O)-H,

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-C(O)-CH₂-T₁-R₁₁,
-C(O)-CH₂-F,
-C=N-O-R₉, and
-CO-Ar₂;

5 each R₅ is independently selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-N(R₁₀)(R₁₀)
10 -S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-CH₂-O-R₉,
-C(O)C(O)-R₁₀,
-R₉,
15 -H,
-C(O)C(O)-OR₁₀, and
-C(O)C(O)-N(R₉)(R₁₀);

Y₂ is H₂ or O;

each T₁ is independently selected from the group 20 consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

R₈ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
25 -C(O)-NH-R₁₀,
-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-CH₂-OR₁₀,
-C(O)C(O)-R₁₀,
30 -C(O)-CH₂-N(R₁₀)(R₁₀),
-C(O)-CH₂C(O)-O-R₉,
-C(O)-CH₂C(O)-R₉,
-H,

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-C(O)-C(O)-OR₁₀, and
-C(O)-C(O)-N(R₉)(R₁₀);

each R₉ is independently selected from the group,
consisting of -Ar₃ and a -C₁₋₆ straight or branched
5 alkyl group optionally substituted with Ar₃, wherein
the -C₁₋₆ alkyl group is optionally unsaturated;

each R₁₀ is independently selected from the group
consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a
-C₁₋₆ straight or branched alkyl group optionally
10 substituted with Ar₃, wherein the -C₁₋₆ alkyl group is
optionally unsaturated;

each R₁₁ is independently selected from the group
consisting of:

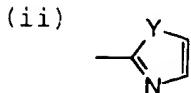
15 -Ar₄,
-(CH₂)₁₋₃-Ar₄,
-H, and
-C(O)-Ar₄;

R₁₅ is selected from the group consisting of -OH,
-OAr₃, -N(H)-OH, and -OC₁₋₆, wherein C₁₋₆ is a straight
20 or branched alkyl group optionally substituted with
Ar₃,
-CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

each R₂₁ is independently selected from the group
consisting of -H or a -C₁₋₆ straight or branched alkyl
25 group;

Ar₂ is independently selected from the following
group, in which any ring may optionally be singly or
multiply substituted by -Q₁ or phenyl, optionally
substituted by Q₁:

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wherein each Y is independently selected from the
5 group consisting of O and S;

each Ar₃ is a cyclic group independently selected
from the set consisting of an aryl group which contains
6, 10, 12, or 14 carbon atoms and between 1 and 3 rings
and an aromatic heterocycle group containing between 5
10 and 15 ring atoms and between 1 and 3 rings, said
heterocyclic group containing at least one heteroatom
group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
-N(R₅)-, and -N(R₉)- said heterocycle group optionally
containing one or more double bonds, said heterocycle
15 group optionally comprising one or more aromatic rings,
and said cyclic group optionally being singly or
multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected
from the set consisting of an aryl group which contains
20 6, 10, 12, or 14 carbon atoms and between 1 and 3
rings, and a heterocycle group containing between 5 and
15 ring atoms and between 1 and 3 rings, said
heterocyclic group containing at least one heteroatom
group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-,
-N(R₅)-, and -N(R₉)- said heterocycle group optionally
25 containing one or more double bonds, said heterocycle
group optionally comprising one or more aromatic rings,
and said cyclic group optionally being singly or
multiply substituted by -Q₁;

30 each Q₁ is independently selected from the group

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consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, -N(R₉)(R₁₀), R₉, -C(O)-R₁₀, and O



provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃;

provided that when:

```

      m is 1;
R1 is (e10);
15 X5 is CH;
R15 is -OH;
R21 is -H; and

```

Y₂ is O and R₃ is -C(O)-H, then R₅ cannot be:
 -C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic group is phenyl, unsubstituted by -Q₁, 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or
 -C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl, unsubstituted by -Q₁; and when

25 γ_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

30 -C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl, 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-

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fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or
-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃ and the Ar₃ cyclic group is phenyl;

5 and when R₁₁ is Ar₄, wherein the Ar₄ cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl, then R₅ cannot be:

-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl;

10 and when R₁₁ is Ar₄, wherein the Ar₄ cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl, then R₅ cannot be:

-C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic group is 4-(dimethylaminomethyl)phenyl, or

15 -C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl, unsubstituted by -Q₁; and when

Y₂ is O, R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, and R₁₁ is -C(O)-Ar₄, wherein the Ar₄ cyclic group is 2,5-dichlorophenyl, then R₅ cannot be:

20 -C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methylphenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-

25 carboethoxy-5-benzimidazolyl, or

-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl, unsubstituted by -Q₁; and when

30 Y₂ is H₂, R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, and R₁₁ is

-C(O)-Ar₄, wherein the Ar₄ cyclic group is 2,5-dichlorophenyl, then R₅ cannot be:

-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃ and the Ar₃

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cyclic group is phenyl.

Compounds of another form of embodiment J (form 2) are those wherein R₂₁ is -CH₃.

5 Compounds of another form of embodiment J (form 3) are those wherein R₅ is -C(O)-C(O)-OR₁₀.

Compounds of another form of embodiment J (form 4) are those wherein R₅ is -C(O)-C(O)-OR₁₀ and R₂₁ is -CH₃.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R₃ is -CO-Ar₂.

10 More preferably, when R₃ is -CO-Ar₂ Y is O.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R₃ is -C(O)-CH₂-T₁-R₁₁ and R₁₁ is -(CH₂)₁₋₃-Ar₄.

15 More preferably, when R₃ is -C(O)-CH₂-T₁-R₁₁ and R₁₁ is -(CH₂)₁₋₃-Ar₄, T₁ is O.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, and R₁₁ is -C(O)-Ar₄.

20 Preferred compounds of embodiments H, I, and J employ formula (V), wherein R₃ is -C(O)-H.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R₃ is -CO-CH₂-T₁-R₁₁ and R₁₁ is -Ar₄.

More preferably, when R₃ is -CO-CH₂-T₁-R₁₁ and

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R₁₁ is -Ar₄, T₁ is O or S.

More preferred compounds of embodiments H and J (forms 1 and 2) are those wherein R₅ is selected from the group consisting of:

- 5 -C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

Alternatively, more preferred compounds of embodiments H and J (forms 1 and 2) are those wherein 10 R₅ is selected from the group consisting of:

- S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉,
15 -C(O)-C(O)-OR₁₀, and
-C(O)-C(O)-N(R₉)(R₁₀).

Most preferably, R₅ is -C(O)-C(O)-R₁₀.

Alternatively, R₅ is -C(O)-C(O)-OR₁₀.

20 More preferred compounds of embodiments H, I (form 2), and J (forms 2 and 4) are those wherein:

m is 1;

25 Y₂ is O;

R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl group optionally substituted with Ar₃, -OH, -OR₉, -CO₂H, 30 wherein the R₉ is a C₁₋₄ branched or straight chain alkyl group; wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

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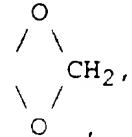
Ar₂ is (hh);

Y is O, and

each Ar₃ cyclic group is independently selected
5 from the set consisting of phenyl, naphthyl, thienyl,
quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,
isoxazolyl, benzotriazolyl, benzimidazolyl,
thienothienyl, imidazolyl, thiadiazolyl,
benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,
10 and said cyclic group optionally being singly or
multiply substituted by -Q₁;

each Ar₄ cyclic group is independently selected
from the group consisting of phenyl, tetrazolyl,
pyridyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl,
15 and said cyclic group optionally being singly or
multiply substituted by -Q₁;

each Q₁ is independently selected from the group
consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
20 -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



25

wherein each R₉ and R₁₀ are independently a -C₁₋₆
straight or branched alkyl group optionally substituted
with Ar₃ wherein the Ar₃ cyclic group is phenyl, and
said cyclic group optionally being singly or multiply
30 substituted by -Q₁;

provided that when -Ar₃ is substituted with a Q₁
group which comprises one or more additional -Ar₃
groups, said additional -Ar₃ groups are not substituted

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with another $-Ar_3$.

More preferred compounds of embodiments I (form 1), and J (form 3) are those wherein:

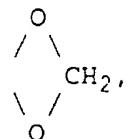
m is 1;

5 R₂₁ is -H or -CH₃;

R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the Ar₃ cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by -Q₁;

10 each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thiienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,
 15 benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
 20 wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



25 wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the Ar₃ cyclic group is phenyl, and
 30 said cyclic group optionally being singly or multiply substituted by -Q₁;

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provided that when -Ar₃ is substituted with a -Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted 5 with another -Ar₃.

Preferably, in these more preferred compounds the Ar₃ cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, 10 benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁.

Preferred compounds of embodiments H, and J (forms 15 1 and 1) are those wherein:

R₃ is -C(O)-CH₂-T₁-R₁₁;
T₁ is O; and

20 R₁₁ is -C(O)-Ar₄, wherein the Ar₄ cyclic group is selected from the set consisting of tetrazolyl, pyridyl, oxazolyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by -Q₁.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R₃ is -CO-CH₂-T₁-R₁₁, R₁₁ is 25 -Ar₄, wherein the Ar₄ cyclic group is pyridyl, and said cyclic group optionally being singly or multiply substituted by -Q₁.

Preferred compounds of embodiment J (form 1) are those wherein:

30 R₃ is -C(O)-H, and

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R₅ is -C(O)-R₁₀, wherein:

R₁₀ is Ar₃, wherein the Ar₃ cyclic group is phenyl optionally being singly or multiply substituted by:

-F,

5 -Cl,

-N(H)-R₅, wherein -R₅ is -H or -C(O)-R₁₀, wherein

R₁₀ is a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl,

10 -N(R₉)(R₁₀), wherein R₉ and R₁₀ are independently a -C₁₋₄ straight or branched alkyl group, or

-O-R₅, wherein R₅ is H or a -C₁₋₄ straight or branched alkyl group.

More preferably, Ar₃ is phenyl being optionally singly or multiply substituted at the 3- or 5-position
15 by -Cl or at the 4-position by -NH-R₅, -N(R₉)(R₁₀), or -O-R₅.

Other more preferred compounds of embodiment J (form 1) are those wherein:

R₃ is -C(O)-H;

20 R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃ cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

25 Other more preferred compounds of embodiment J (form 1) are those wherein:

R₃ is -C(O)-H;

R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃

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cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁.

Other more preferred compounds of embodiment J
5 (form 1) are those wherein:

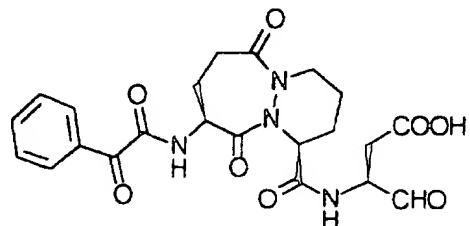
R₃ is -C(O)-H;

R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃ cyclic group is phenyl, substituted by

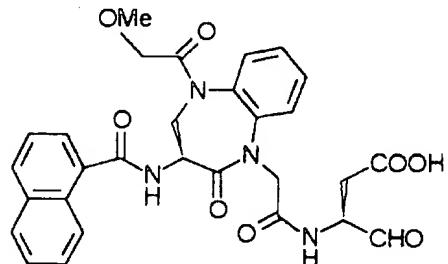


Preferred compounds of embodiment (J)
15 include, but are not limited to:

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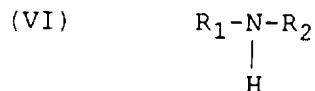
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The ICE inhibitors of another embodiment (K) of this invention are those of formula:

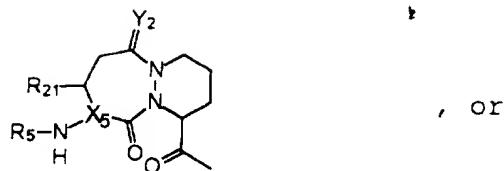
5



wherein:

R_1 is:

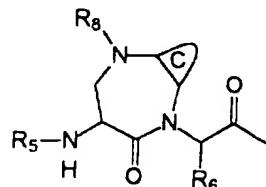
(e10)



, or

10

(w2)



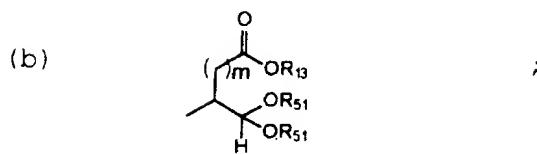
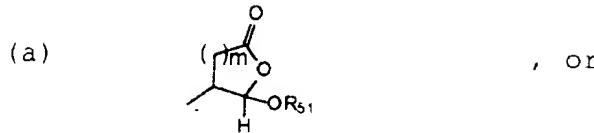
;

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl; the ring optionally being singly or multiply substituted by $-Q_1$;

15

R_2 is:

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m is 1 or 2;

5 each R₅ is independently selected from the group consisting of:

-C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-N(R₁₀)(R₁₀)

10 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-O-R₉,
 -C(O)C(O)-R₁₀,

15 -R₉,
 -H,
 -C(O)C(O)-OR₁₀, and
 -C(O)C(O)-N(R₉)(R₁₀);

X₅ is CH or N;

20 Y₂ is H₂ or O;

R₆ is selected from the group consisting of -H and -CH₃;

25 R₈ is selected from the group consisting of:

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-C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-N(H)-R₁₀,
-S(O)₂-R₉,
5 -S(O)₂-NH-R₁₀,
-C(O)-CH₂-OR₁₀,
-C(O)C(O)-R₁₀;
-C(O)-CH₂N(R₁₀)(R₁₀),
-C(O)-CH₂C(O)-O-R₉,
10 -C(O)-CH₂C(O)-R₉,
-H, and
-C(O)-C(O)-OR₁₀;

each R₉ is independently selected from the group
consisting of -Ar₃ and a -C₁₋₆ straight or branched
15 alkyl group optionally substituted with Ar₃, wherein
the -C₁₋₆ alkyl group is optionally unsaturated;

each R₁₀ is independently selected from the group
consisting of -H, -Ar₃, a -C₃₋₆ cycloalkyl group, and a
-C₁₋₆ straight or branched alkyl group optionally
20 substituted with Ar₃, wherein the -C₁₋₆ alkyl group is
optionally unsaturated;

R₁₃ is selected from the group consisting of H,
Ar₃, and a -C₁₋₆ straight or branched alkyl group
optionally substituted with Ar₃, -CONH₂, -OR₅, -OH,
25 -OR₉, or -CO₂H;

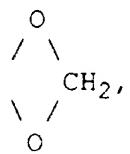
each R₅₁ is independently selected from the group
consisting of R₉, -C(O)-R₉, -C(O)-N(H)-R₉, or each R₅₁
taken together forms a saturated 4-8 member carbocyclic
ring or heterocyclic ring containing -O-, -S-, or -NH-;

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each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected
5 from the set consisting of an aryl group which contains
6, 10, 12, or 14 carbon atoms and between 1 and 3 rings
and an aromatic heterocycle group containing between 5
and 15 ring atoms and between 1 and 3 rings, said
heterocyclic group containing at least one heteroatom
10 group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, and $-NH-$,
said heterocycle group optionally containing one or
more double bonds, said heterocycle group optionally
comprising one or more aromatic rings, and said cyclic
group optionally being singly or multiply substituted
15 by $-Q_1$;

each Q_1 is independently selected from the group
consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$,
20 $=O$, $-OH$, -perfluoro C_{1-3} alkyl, R_5 , $-OR_5$, $-NHR_5$, $-OR_9$,
 $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and



25

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

30 Preferred compounds of this embodiment are those
wherein:

m is 1;

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C is a ring chosen from the set consisting of benzo, pyrido, or thieno the ring optionally being singly or multiply substituted by halogen, -NH₂, -NH-R₅, -NH-R₉, -OR₁₀, or -R₉, wherein R₉ is a straight or branched C₁₋₄ alkyl group and R₁₀ is H or a straight or branched C₁₋₄ alkyl group;

R₆ is H;

R₁₃ is H or a C₁₋₄ straight or branched alkyl group optionally substituted with Ar₃, -OH, -OR₉, -CO₂H, wherein the R₉ is a C₁₋₄ branched or straight chain alkyl group; wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

R₂₁ is -H or -CH₃;

R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thiienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, 20 isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

25 each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and

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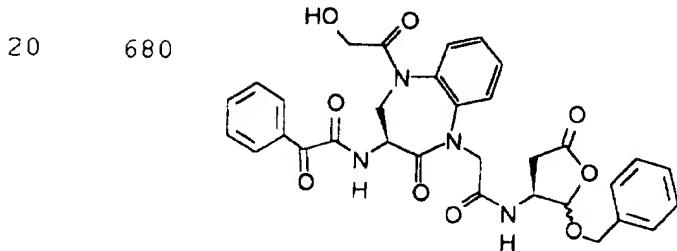
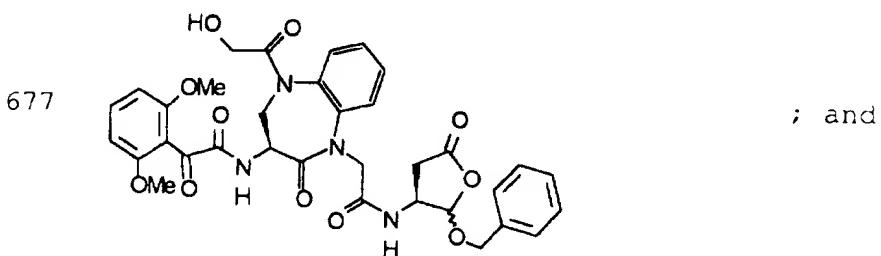


wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

10 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

15 Preferably, in this preferred embodiment, R₁ is (w2) and the other substituents are as defined above.

Compounds of this preferred embodiment include, but are not limited to:



More preferably, R₈ is selected from the

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group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-CH₂-OR₁₀, and
5 -C(O)-CH₂C(O)-R₉.

Most preferably, R₈ is -C(O)-CH₂-OR₁₀ and R₁₀ is -H or -CH₃.

Alternatively, in this preferred embodiment, R₁ is (e10) and X₅ is CH and the other substituents are 10 as defined above.

Alternatively, in this preferred embodiment, R₁ is (e10) and X₅ is N and the other substituents are as defined above.

15 Preferably, in any of the above compounds of embodiment (K), R₅ is -C(O)-R₁₀ or -C(O)-C(O)-R₁₀ and the other substituents are as defined above.

More preferably, R₁₀ is -Ar₃ and the other substituents are as defined above.

20 More preferably, in these more preferred compounds:

R₅ is -C(O)-R₁₀ and R₁₀ is Ar₃,

wherein the Ar₃ cyclic group is phenyl optionally being singly or multiply substituted by:

25 -R₉, wherein R₉ is a C₁₋₄ straight or branched alkyl group;

-F,

-Cl,

30 -N(H)-R₅, wherein -R₅ is -H or -C(O)-R₁₀, wherein R₁₀ is a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl,

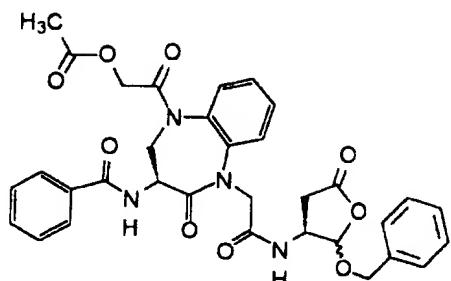
-N(R₉)(R₁₀), wherein R₉ and R₁₀ are independently a -C₁₋₄ straight or branched alkyl group, or

-O-R₅, wherein R₅ is H or a -C₁₋₄ straight or branched alkyl group.

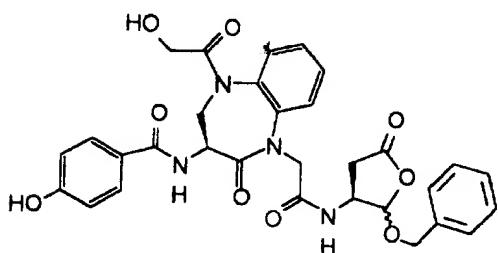
- 208 -

Preferred compounds of this more preferred embodiment include, but are not limited to:

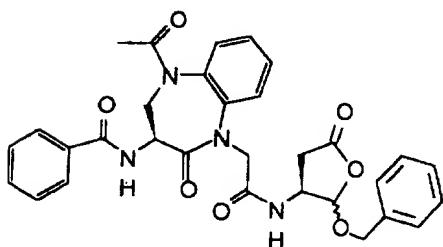
682 ;



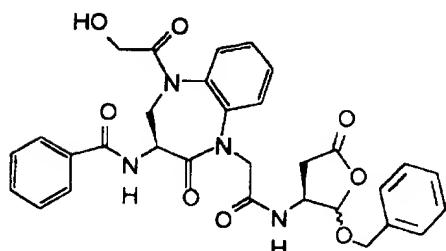
690b ;



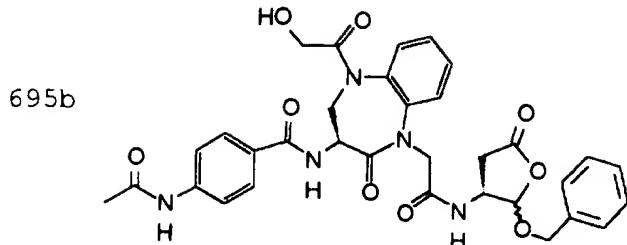
5 693 ;



695a ;



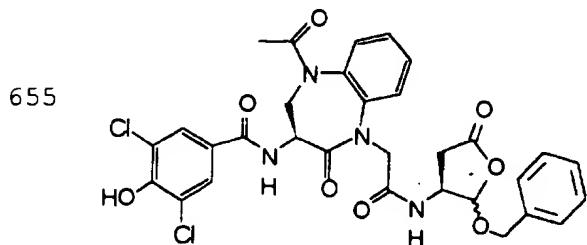
- 209 -



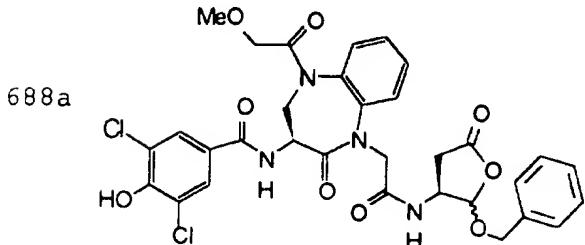
Most preferably, Ar₃ is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R₅, -N(R₉)(R₁₀), or -O-R₅.

5

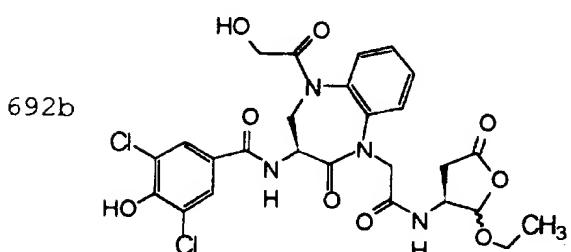
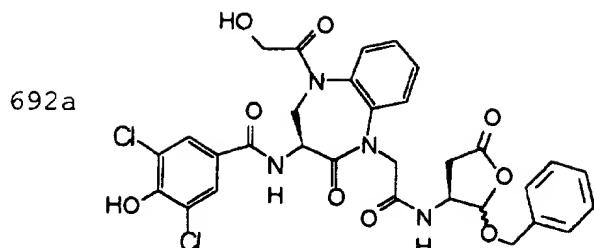
Preferred compounds of this most preferred embodiment include, but are not limited to:



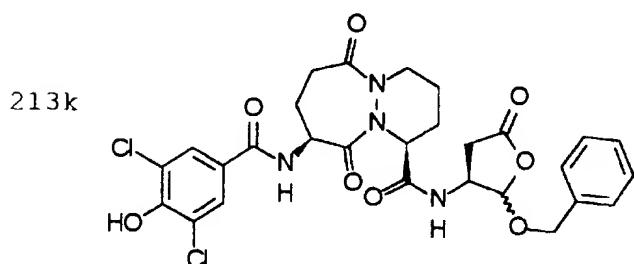
10



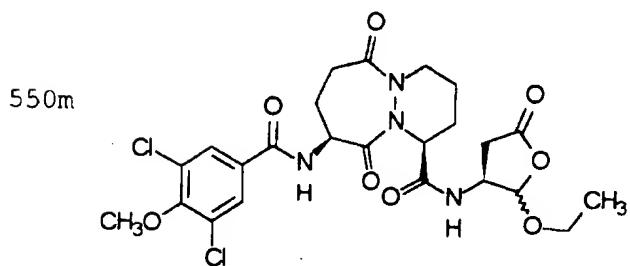
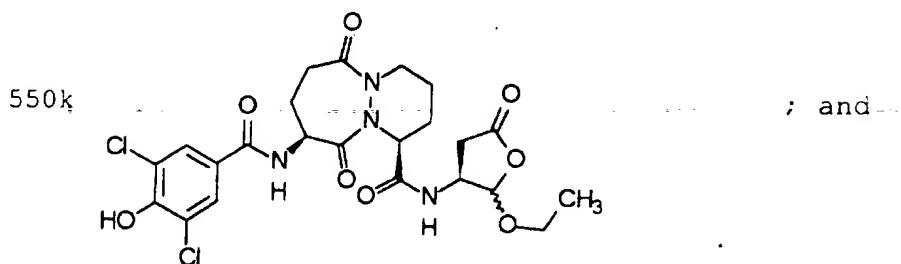
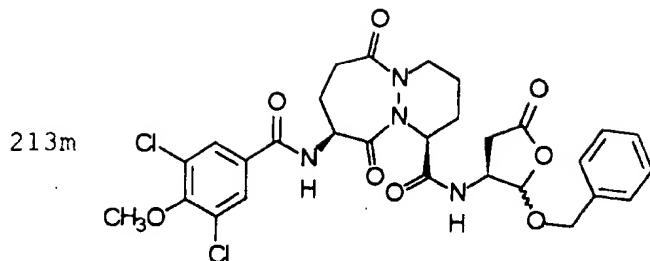
- 210 -



Other preferred compounds of
this most preferred embodiment include, but are not
5 limited to:



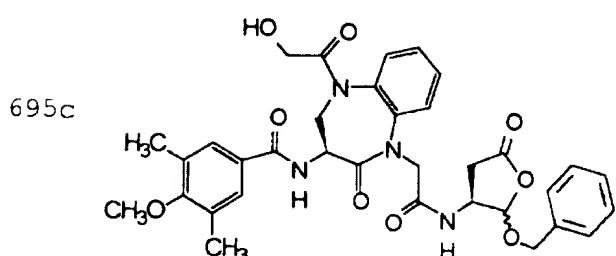
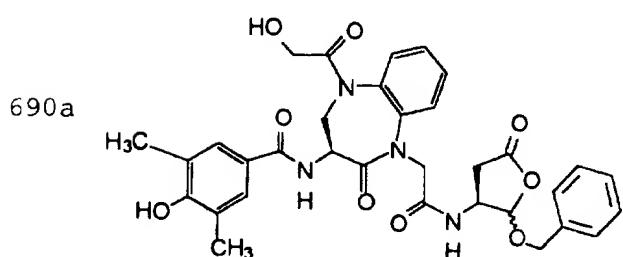
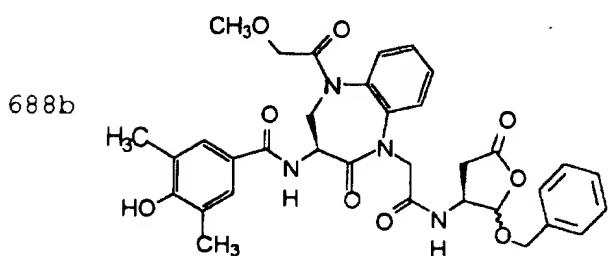
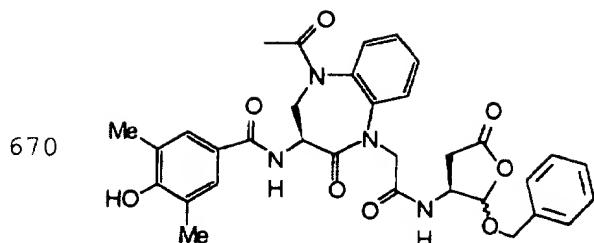
- 211 -



Alternatively, Ar₃ is phenyl being
5 singly or multiply substituted at the 3- or 5-position
by -R₉, wherein R₉ is a C₁₋₄ straight or branched alkyl
group; and at the 4-position by -O-R₅.

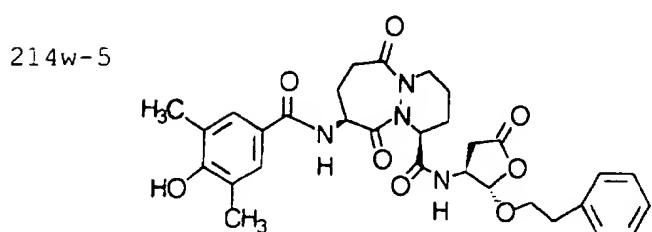
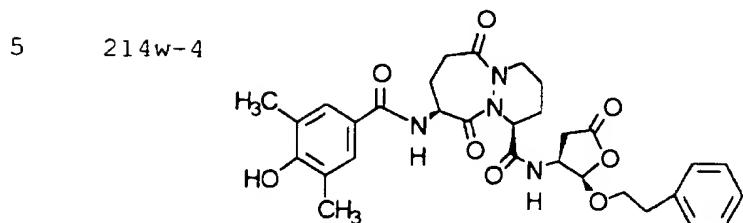
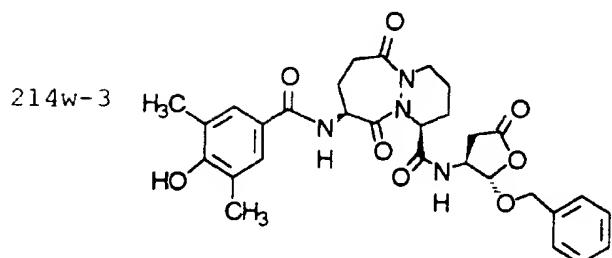
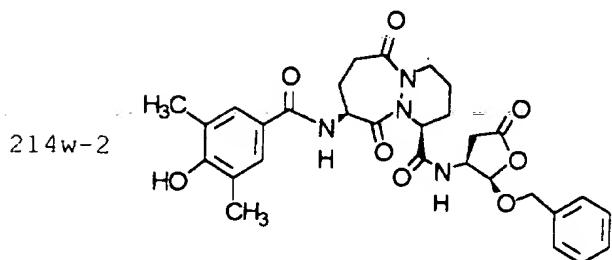
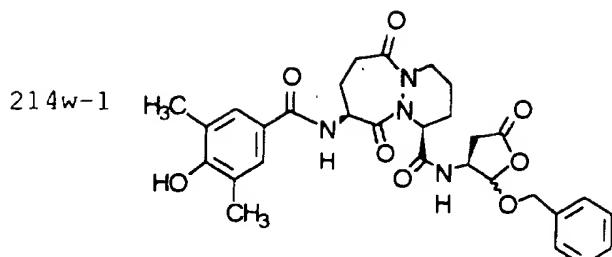
Preferred compounds of this
most preferred embodiment include, but are not limited
10 to:

- 212 -

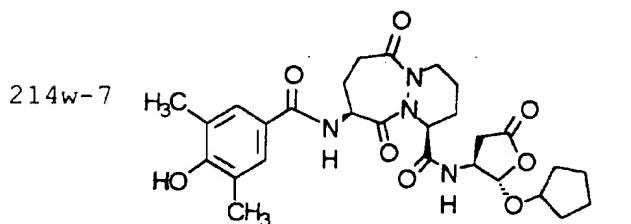
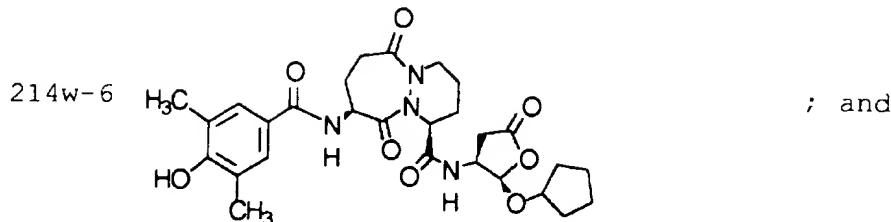


- 213 -

limited to:



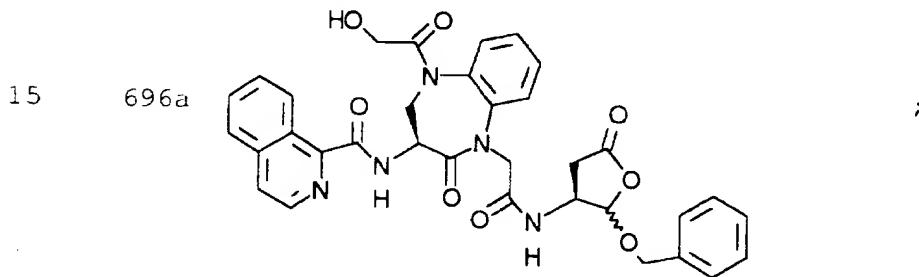
- 214 -



Alternatively, in this more preferred embodiment, R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the 5 Ar₃ cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q₁.

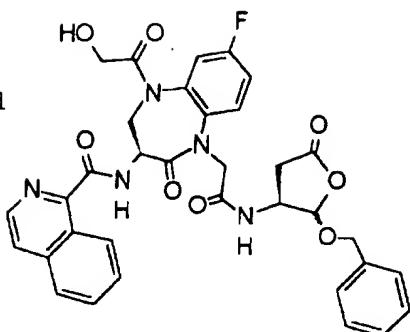
10 Most preferably, the Ar₃ cyclic group is isoquinolyl.

Preferred compounds of this most preferred embodiment include, but are not limited to:

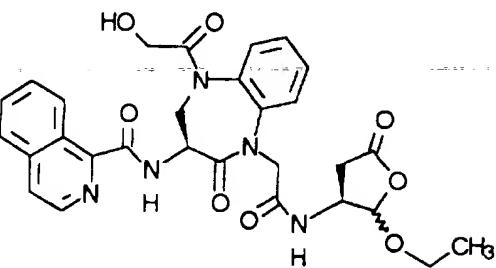


- 215 -

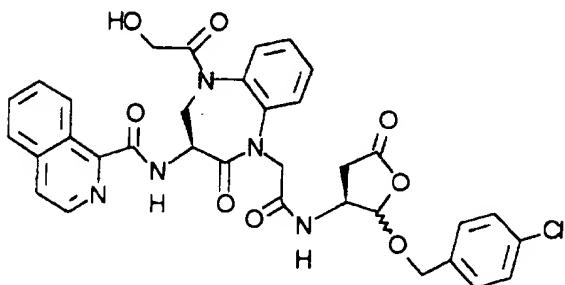
696a-1



696b

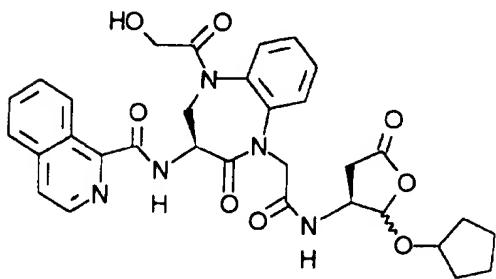


696c

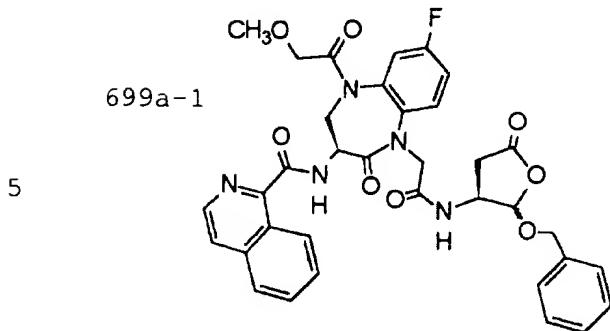
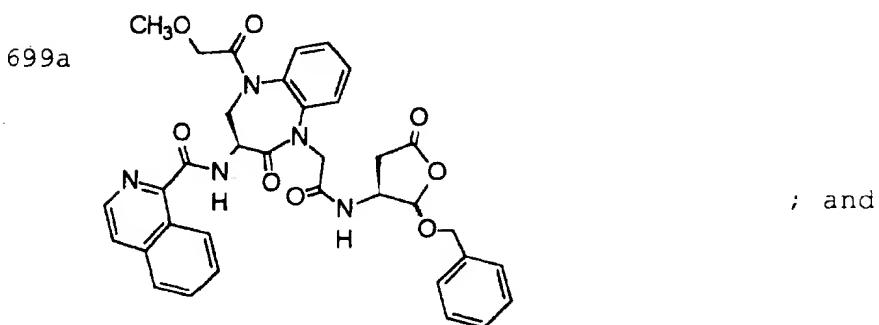
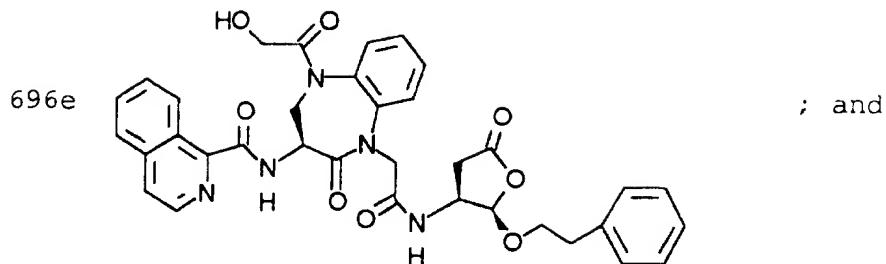


5

696d



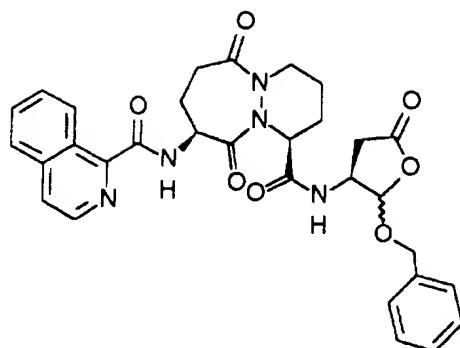
- 216 -



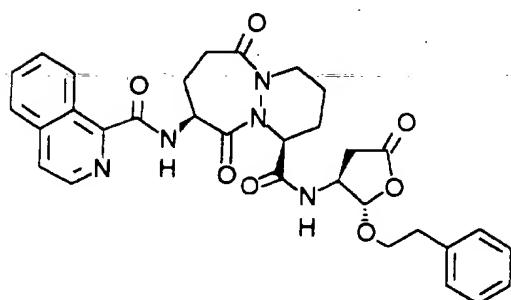
Other preferred compounds of
this most preferred embodiment include, but are not
limited to:

- 217 -

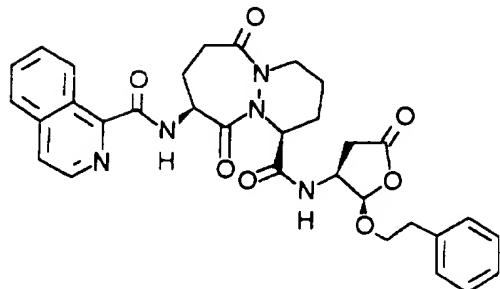
213y



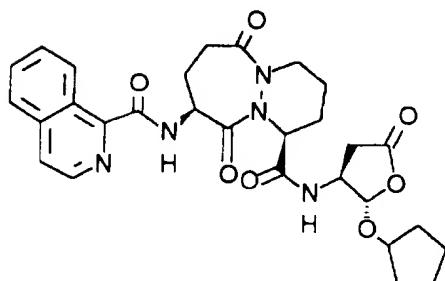
412a



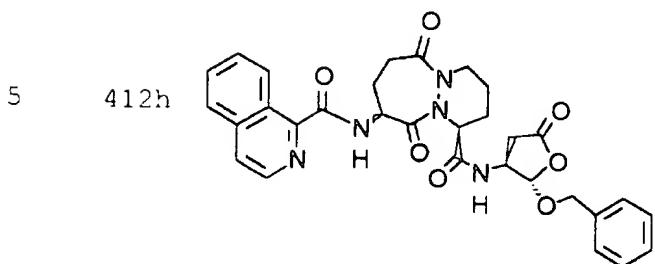
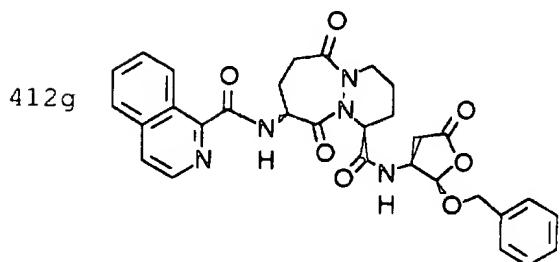
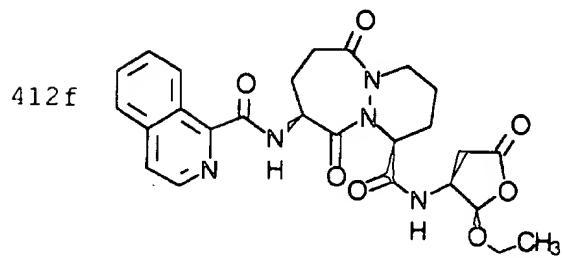
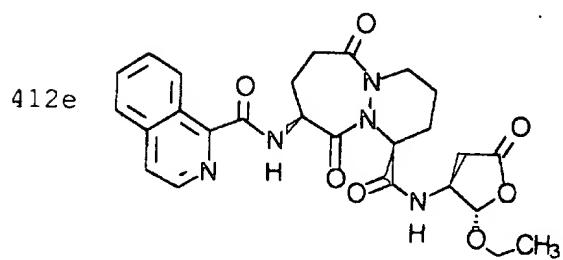
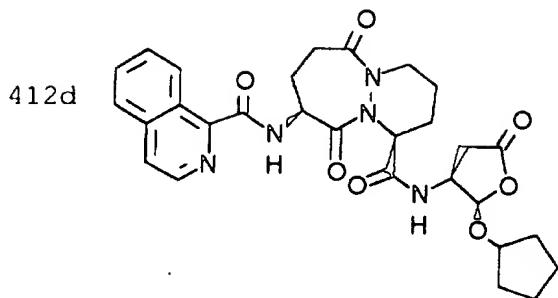
412b



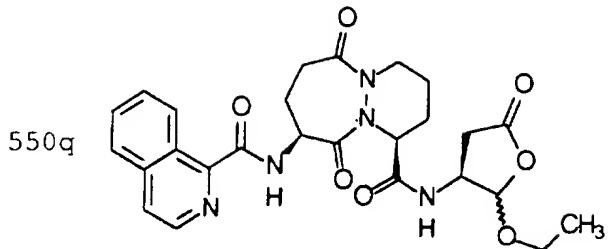
412c



- 218 -

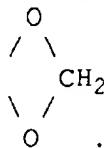


- 219 -



Alternatively, in this more preferred embodiment, R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃ cyclic group is phenyl, substituted by

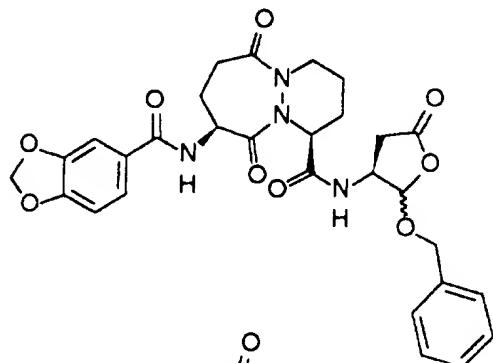
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10

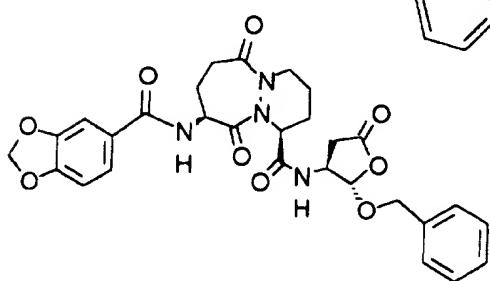
Preferred compounds of this more preferred embodiment include, but are not limited to:

213n



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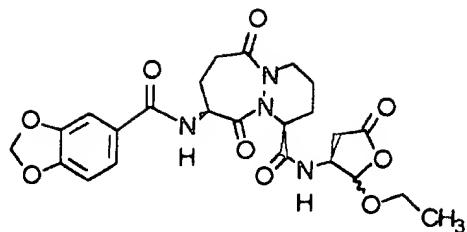
415a



;

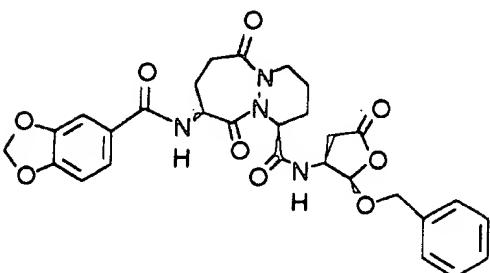
- 220 -

415b



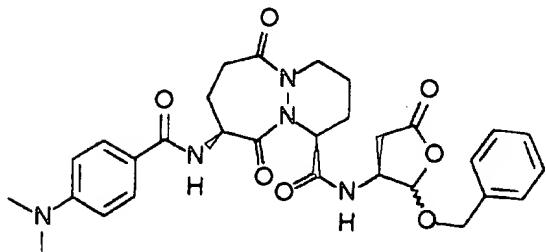
; and

415c



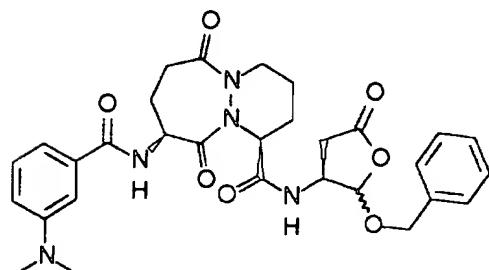
Other compounds of embodiment (K) include,
5 but are not limited to:

213f



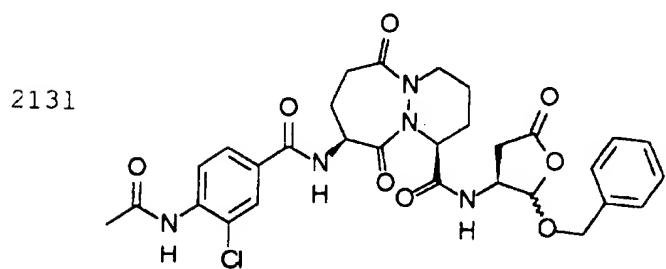
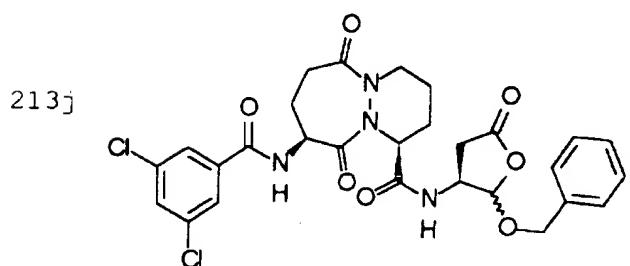
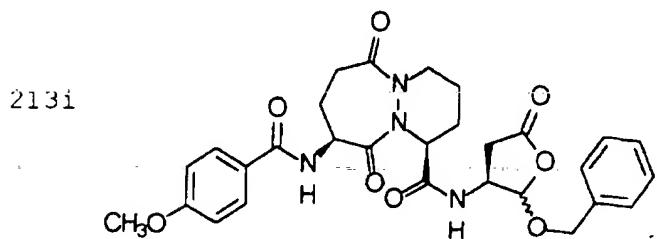
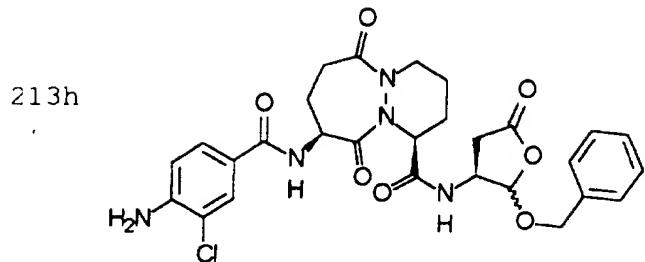
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213g



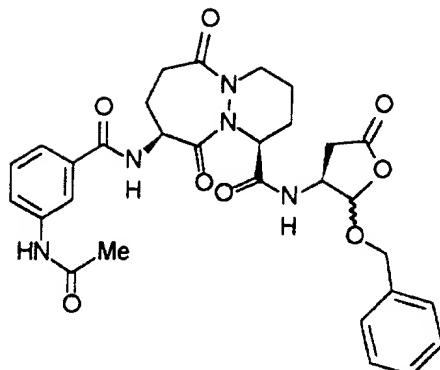
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- 221 -

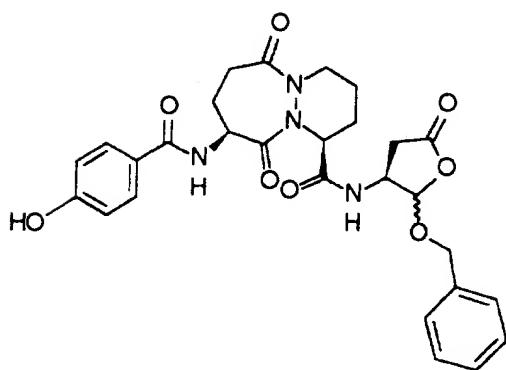


- 222 -

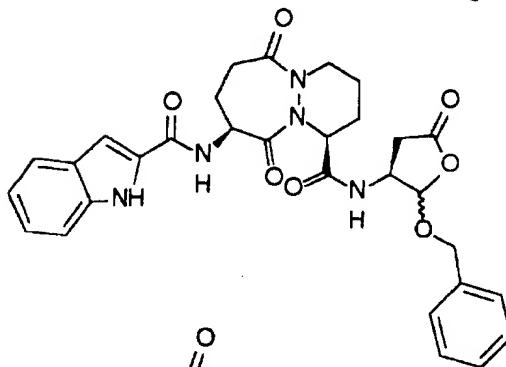
213o



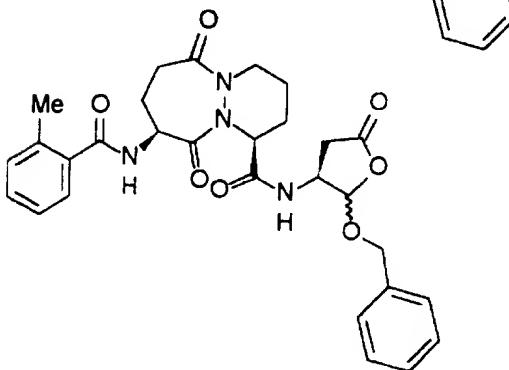
213p



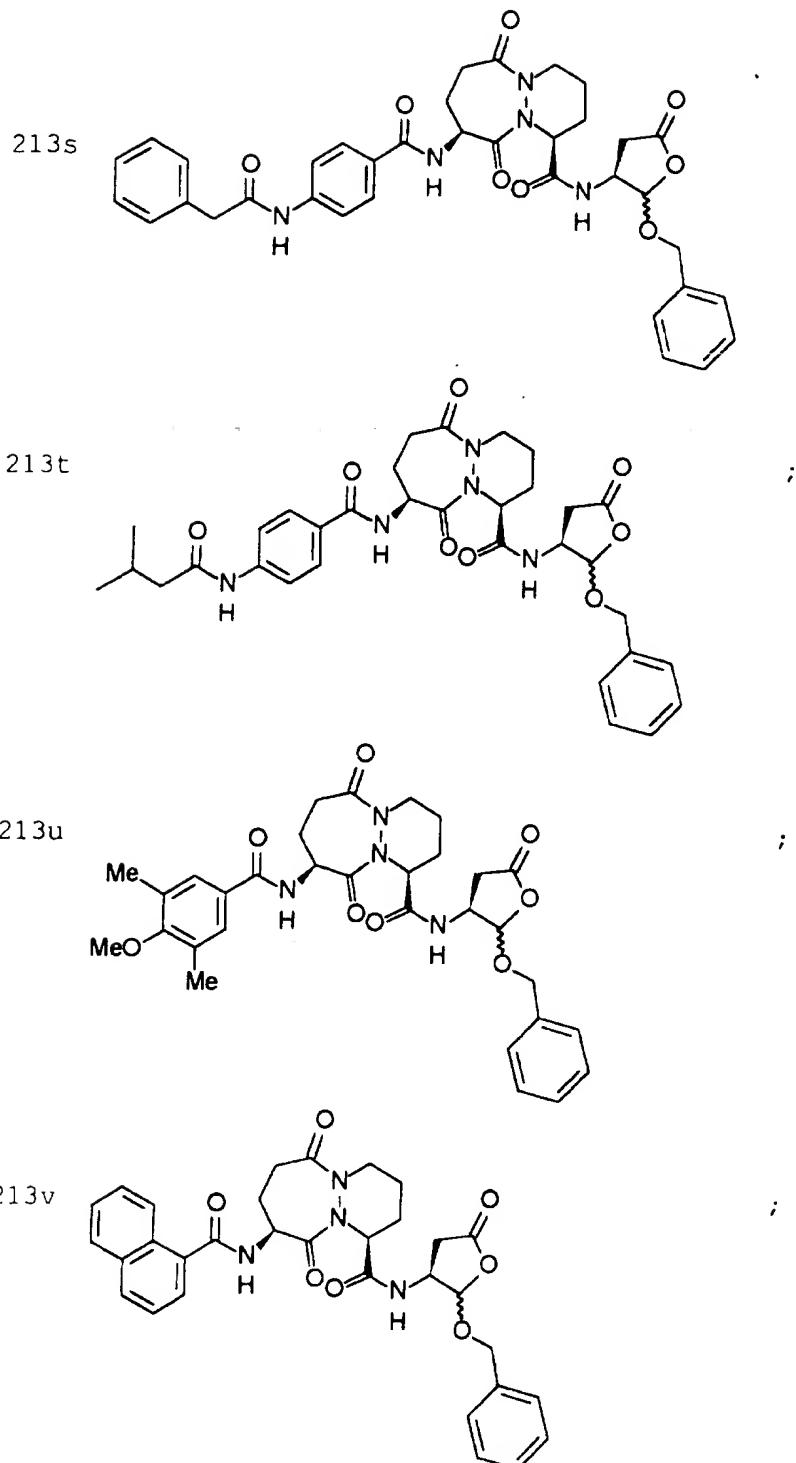
213q



213r

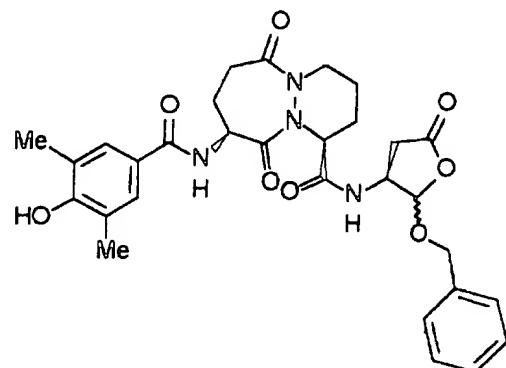


- 223 -



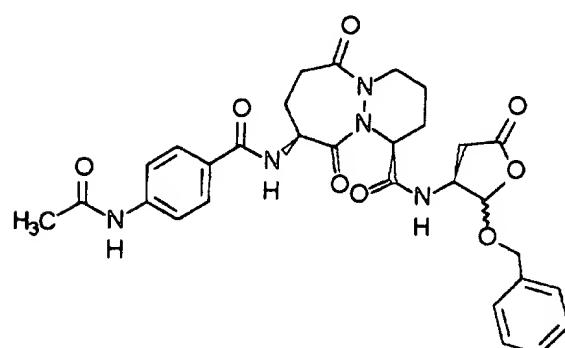
- 224 -

213w



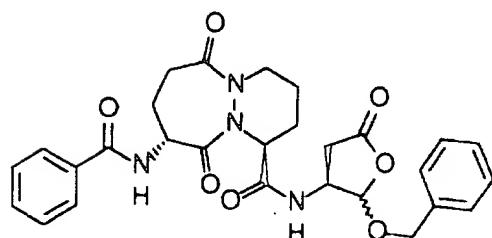
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213x



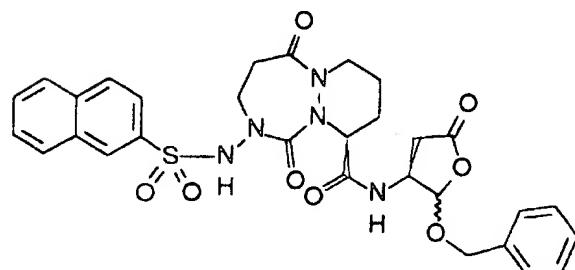
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245b



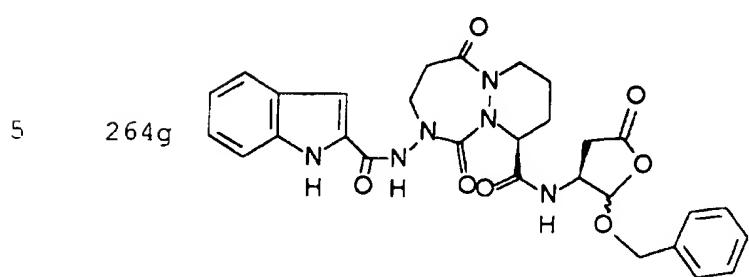
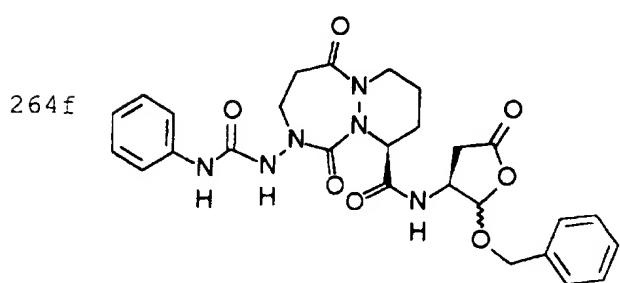
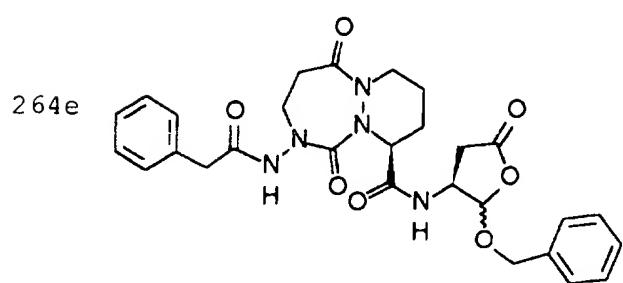
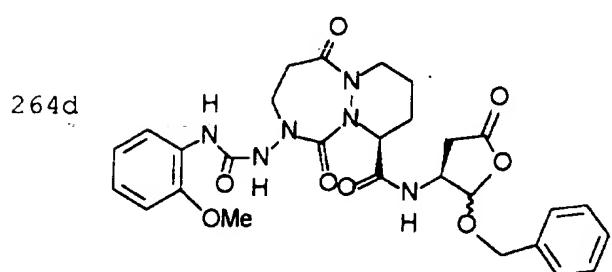
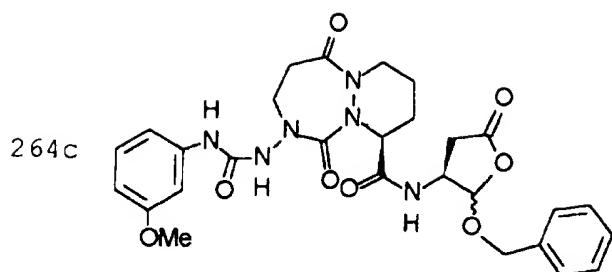
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264a

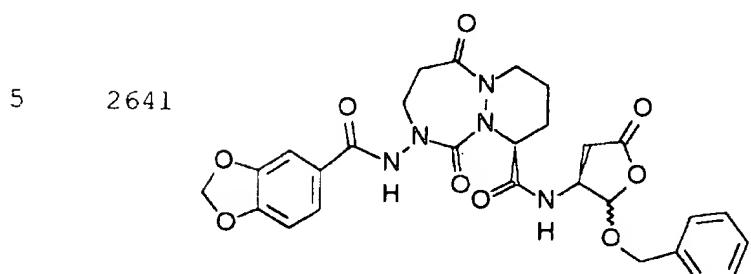
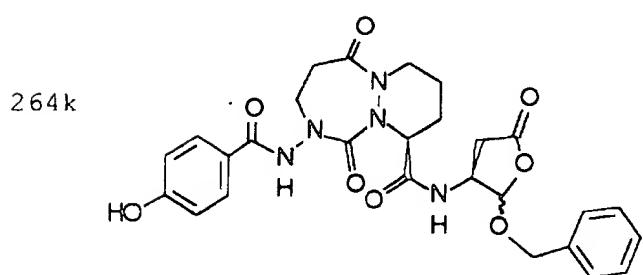
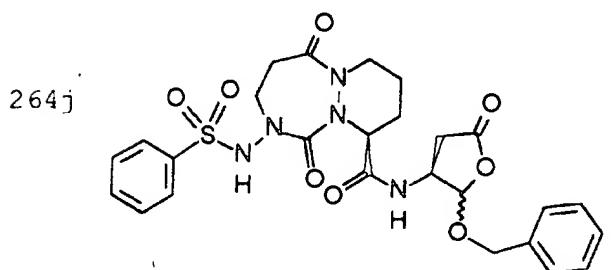
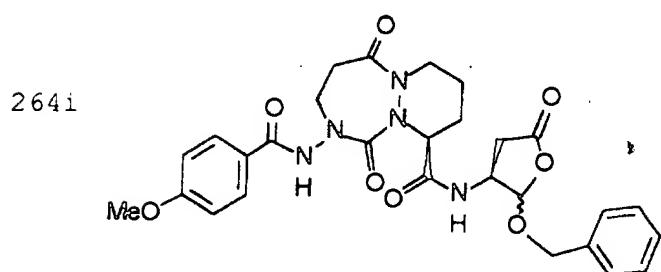
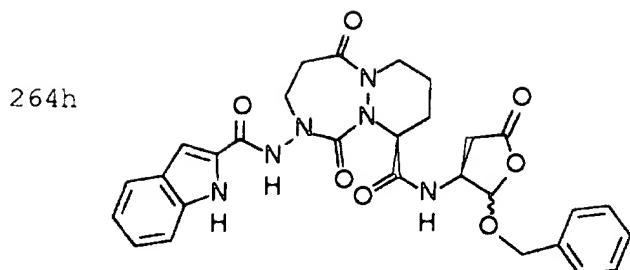


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- 225 -

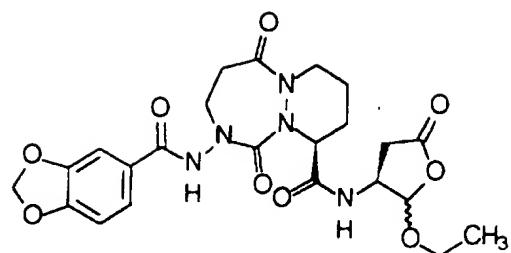


- 226 -

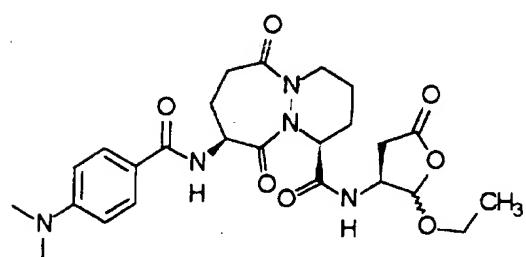


- 227 -

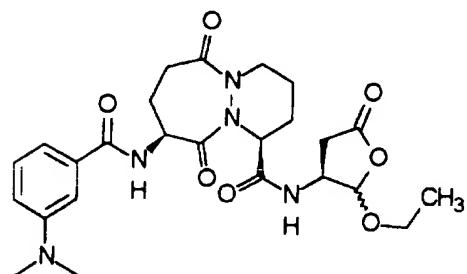
528 ;



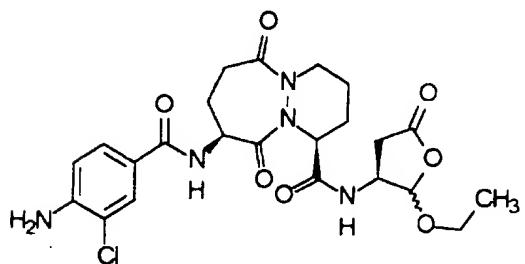
550f ;



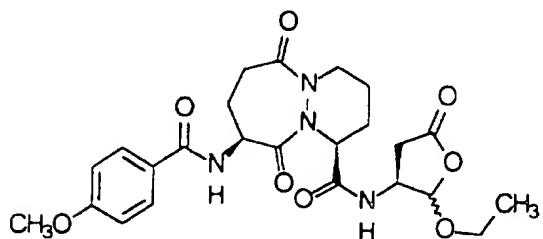
550g ;



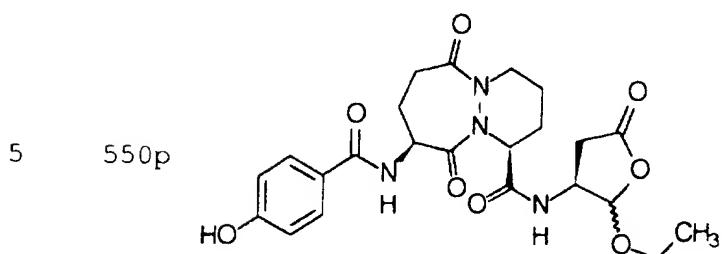
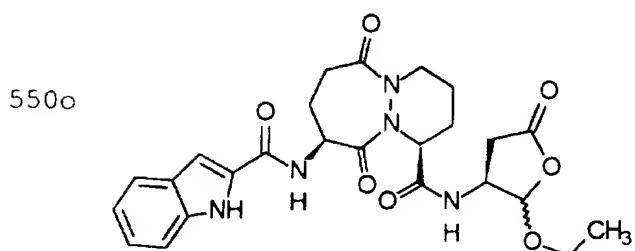
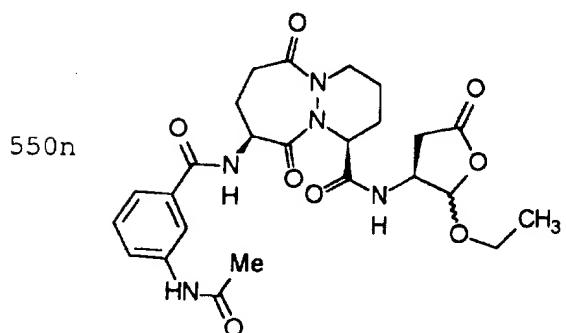
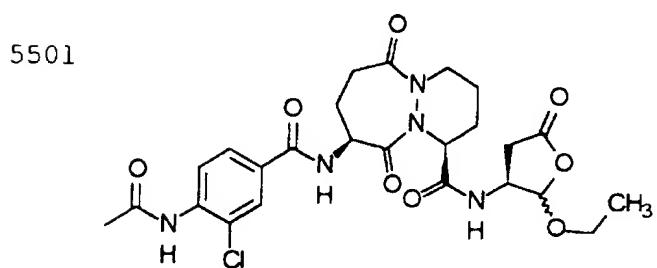
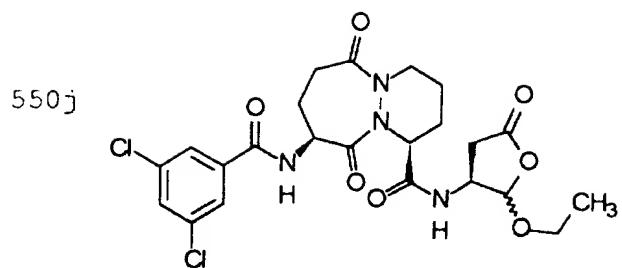
550h ;

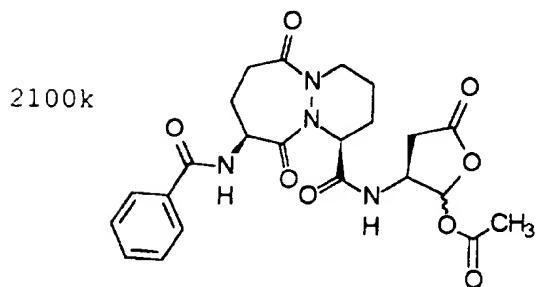
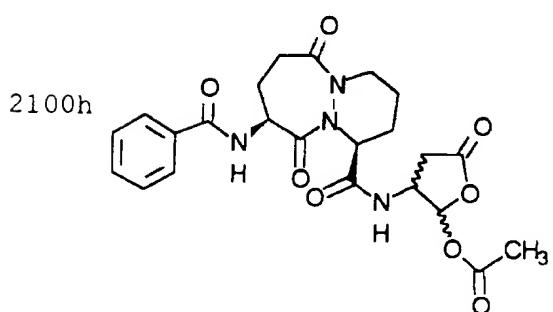
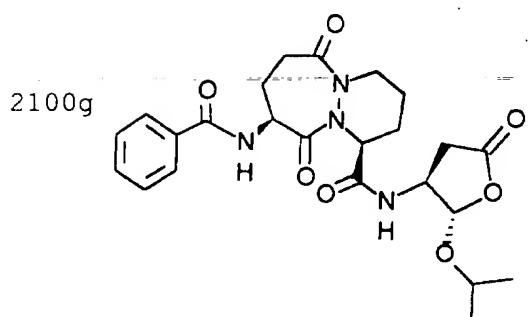
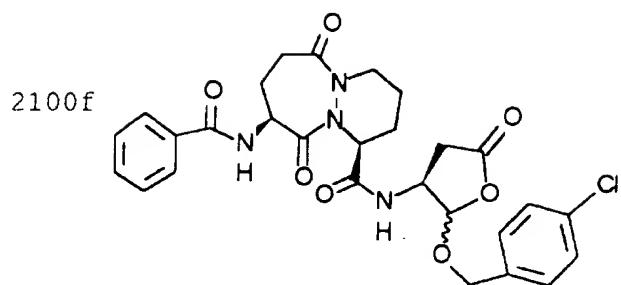


5 550i ;

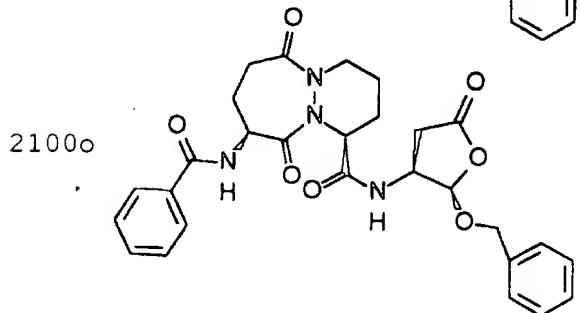
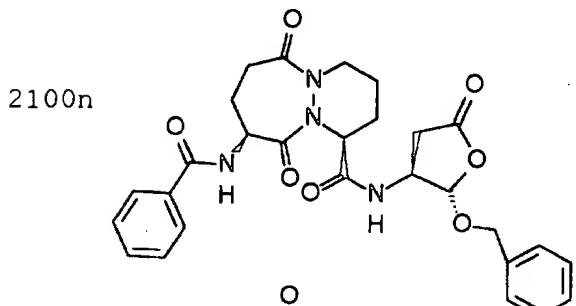
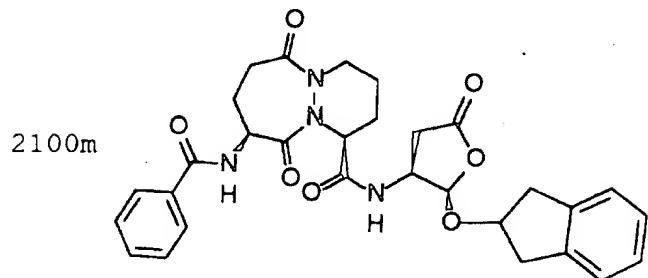
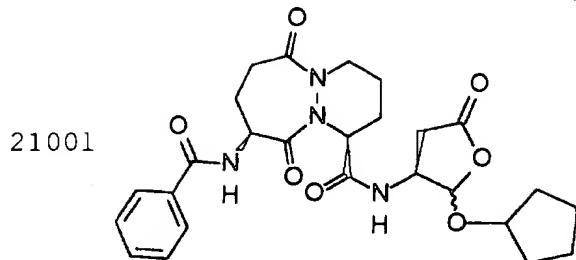


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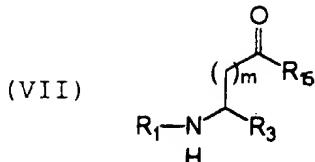
- 230 -



5

The ICE inhibitors of another embodiment (L)
of this invention are those of formula :

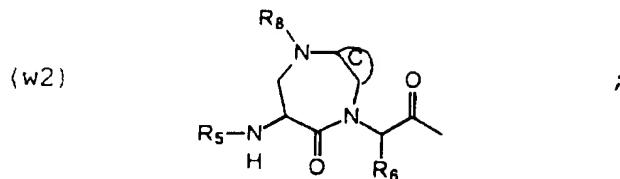
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wherein:

m is 1 or 2;

5 R₁ is selected from the group consisting of the following formulae:



10 C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being singly or multiply substituted by -Q₁;

15 R₃ is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH₂-T₁-R₁₁,
- C(O)-CH₂-F,

20 -C=N-O-R₉, and
-CO-Ar₂;

each R₅ is independently selected from the group consisting of:

25 -C(O)-R₁₀,
-C(O)O-R₉,

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-C(O)-N(R₁₀)(R₁₀)
-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-CH₂-O-R₉,
5 -C(O)C(O)-R₁₀,
-R₉,
-H,
-C(O)C(O)-OR₁₀, and
-C(O)C(O)-N(R₉)(R₁₀);

10

each T₁ is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

15 R₆ is selected from the group consisting of -H and -CH₃;

R₈ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-NH-R₁₀,
20 -S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-CH₂-OR₁₀,
-C(O)C(O)-R₁₀,
-C(O)-CH₂-N(R₁₀)(R₁₀),
25 -C(O)-CH₂C(O)-O-R₉,
-C(O)-CH₂C(O)-R₉,
-H, and
-C(O)-C(O)-OR₁₀;

30 each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

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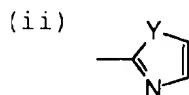
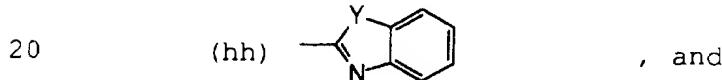
each R_{10} is independently selected from the group consisting of -H, - Ar_3 , a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar_3 , wherein the -C₁₋₆ alkyl group is 5 optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

- Ar_4 ,
- $(CH_2)_{1-3}Ar_4$,
- 10 -H, and
- C(O)- Ar_4 ;

R_{15} is selected from the group consisting of -OH, -O Ar_3 , -N(H)-OH, and -OC₁₋₆, wherein C₁₋₆ is a straight or branched alkyl group optionally substituted with 15 Ar_3 , -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ or phenyl, optionally substituted by Q₁:



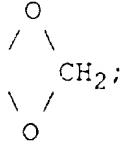
wherein each Y is independently selected from the group consisting of O and S;

25 each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains

- 234 -

6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom
 5 group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or
 10 multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and
 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom
 15 group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or
 20 multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN,
 25 =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, -OR₉, -N(R₉)(R₁₀), -R₉, -C(O)-R₁₀, and
 30


provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃

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groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferably,

m is 1;

5 C is a ring chosen from the set consisting of benzo, pyrido, and thieno, the ring optionally being singly or multiply substituted by halogen, $-NH_2$, $-NH-R_5$, or $-NH-R_9$, $-OR_{10}$, or $-R_9$, wherein R_9 is a straight or branched $-C_{1-4}$ alkyl group, and R_{10} is $-H$ or
10 a straight or branched $-C_{1-4}$ alkyl group;

T_1 is O or S;

R_6 is H;

15 R_{11} is selected from the group consisting of $-Ar_4$, $-(CH_2)_{1-3}-Ar_4$, and $-C(O)-Ar_4$;

Ar_2 is (hh);

Y is O;

20 each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thieryl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;
25

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,

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naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

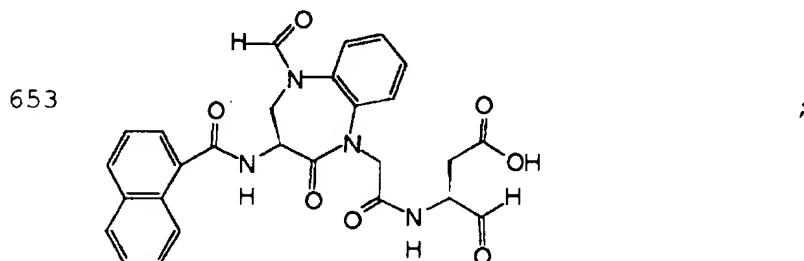
each Q₁ is independently selected from the group
 5 consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
 wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
 -C(O)-R₁₀, -OR₉, -NHR₉, and

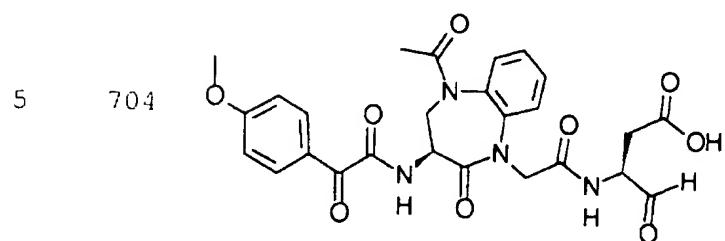
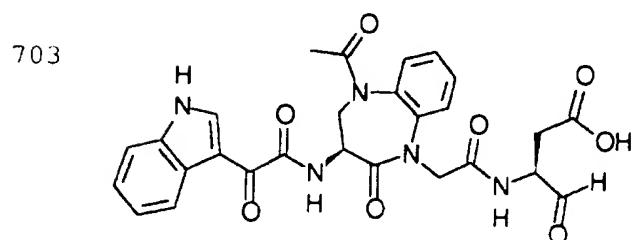
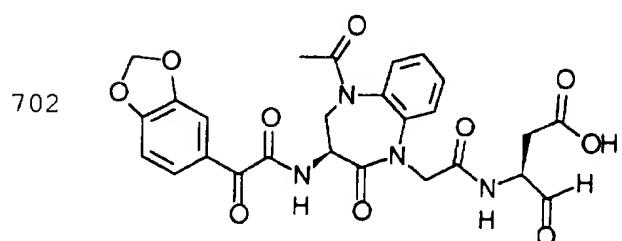
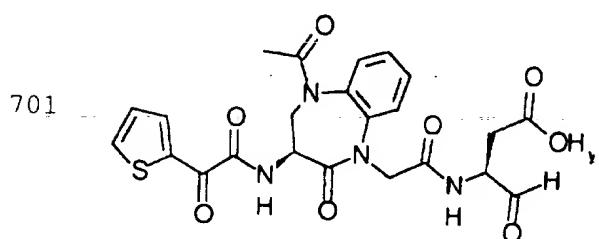
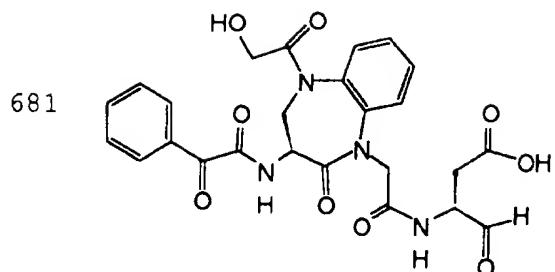


wherein each R₉ and R₁₀ are independently a -C₁₋₆
 straight or branched alkyl group optionally substituted
 15 with -Ar₃ wherein Ar₃ is phenyl;

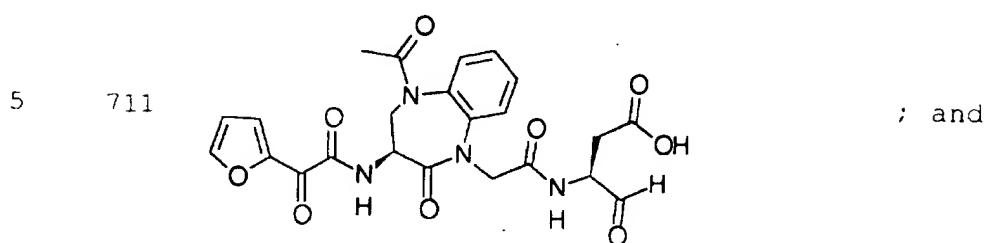
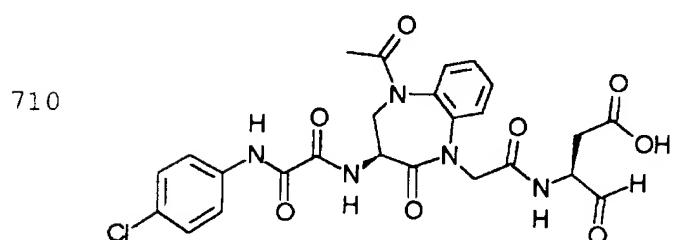
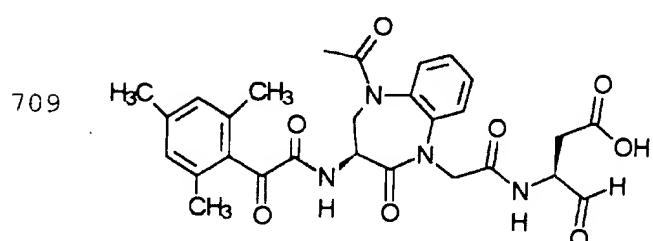
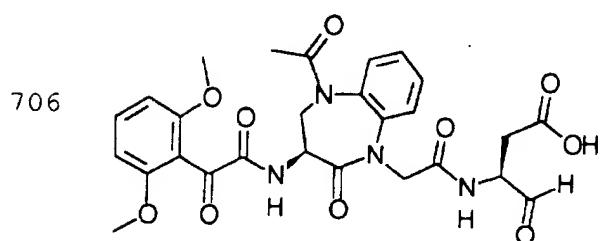
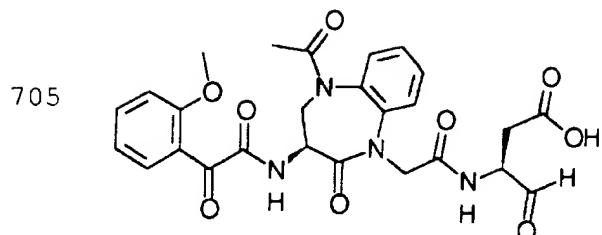
provided that when -Ar₃ is substituted with a Q₁
 group which comprises one or more additional -Ar₃
 groups, said additional -Ar₃ groups are not substituted
 20 with another -Ar₃.

Preferred compounds of this
 preferred embodiment include, but are not limited to:

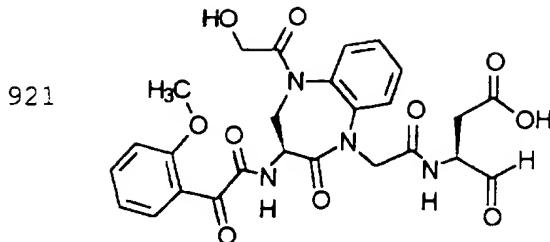




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More preferably, R_3 is $-C(O)-Ar_2$
and the other substituents are as described above.

Alternatively, R_3 is

15 $-C(O)CH_2-T_1-R_{11}$;

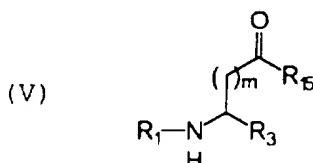
Alternatively, R_3 is $-C(O)-H$.

Preferably, in any of the above compounds of embodiment (L), R_8 is selected from the group consisting of:

10 $-C(O)-R_{10}$,
 $-C(O)O-R_9$,
 $-C(O)-CH_2-OR_{10}$, and
 $-C(O)-CH_2C(O)-R_9$.

More preferably, R_8 is $-C(O)-CH_2-OR_{10}$ and
15 R_{10} is $-H$ or $-CH_3$.

Alternatively, ICE inhibitors of embodiment (L) of this invention are those of formula :

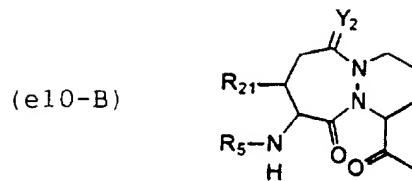


wherein:

20 m is 1;

R_1 is:

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;

R₃ is selected from the group consisting of:

- CN,
- 5 -C(O)-H,
- C(O)-CH₂-T₁-R₁₁,
- C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

10 each R₅ is independently selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- 15 -S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-CH₂-O-R₉,
- C(O)C(O)-R₁₀,
- R₉,
- 20 -H,
- C(O)C(O)-OR₁₀, and
- C(O)C(O)-N(R₉)(R₁₀);

Y₂ is H₂ or O;

25 each T₁ is independently selected from the group consisting of -O- or -S-;

each R₉ is independently selected from the group

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consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

5 each R₁₀ is independently selected from the group consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

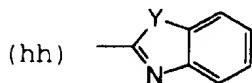
10 each R₁₁ is independently selected from the group consisting of:

-Ar₄,
-(CH₂)₁₋₃-Ar₄,
-H, and
-C(O)-Ar₄;

15 R₁₅ is selected from the group consisting of -OH, -OAr₃, -N(H)-OH, and -OC₁₋₆, wherein C₁₋₆ is a straight or branched alkyl group optionally substituted with -Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

R₂₁ is -H or -CH₃;

20 Ar₂ is:



wherein Y is O;

each Ar₃ is a cyclic group independently selected from the set consisting of phenyl, naphthyl, thieryl,
25 quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,

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isoxazolyl, benzotriazolyl, benzimidazolyl,
thienothienyl, imidazolyl, thiadiazolyl,
benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl,
and said cyclic group optionally being singly or
5 multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected
from the set consisting of phenyl, tetrazolyl,
pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and
thienyl, and said cyclic group optionally being singly
10 or multiply substituted by -Q₁;

each Q₁ is independently selected from the group
consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
-C(O)-R₁₀, -OR₉, -NHR₉, and



20 provided that when -Ar₃ is substituted with a Q₁
group which comprises one or more additional -Ar₃
groups, said additional -Ar₃ groups are not substituted
with another -Ar₃;

provided that when:

25 m is 1;
R₁₅ is -OH;
R₂₁ is -H; and

Y₂ is O and R₃ is -C(O)-H, then R₅ cannot be:
-C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic

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group is phenyl, unsubstituted by $-Q_1$, 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

5 $-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl, then R_5 cannot be:

10 -H;

- $C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl, 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

15 $-C(O)-OR_9$, wherein R_9 is isobutyl or $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl; and when R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl or 5-(1-(4-chloro-2-pyridinyl)-3-trifluoromethyl)pyrazolyl, then 20 R_5 cannot be:

- $C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl;

25 and when R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl, then R_5 cannot be:

- $C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, or

30 - $C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

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Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

5 $-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methylphenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-
10 carboethoxy-5-benzimidazolyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

15 Y_2 is H₂, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl.

20 Preferably, in any of the above compounds of embodiment (L), R_3 is $-C(O)-H$ and R_5 is $-C(O)-R_{10}$ or
- $C(O)-C(O)-R_{10}$ and the other substituents are as defined above.

More preferably R_{10} is $-Ar_3$ and the other substituents are as defined above.

25 More preferably in these more preferred compounds:

R_5 is $-C(O)-R_{10}$ and R_{10} is Ar_3 , wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

30 $-R_9$, wherein R_9 is a C₁₋₄ straight or branched alkyl group;

 -F,

 -Cl,

 -N(H)- R_5 , wherein $-R_5$ is -H or $-C(O)-R_{10}$,

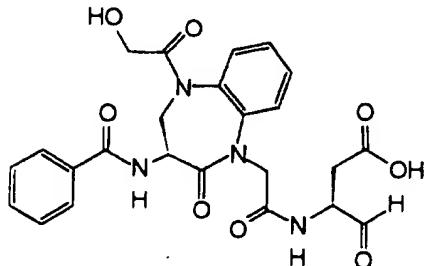
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wherein R₁₀ is a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl,

- 5 -N(R₉)(R₁₀), wherein R₉ and R₁₀ are independently a -C₁₋₄ straight or branched alkyl group, or
 -O-R₅, wherein R₅ is H or a -C₁₋₄ straight or branched alkyl group.

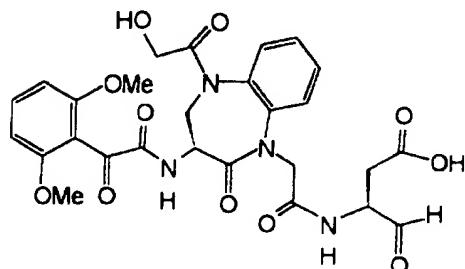
Preferred compounds of this preferred embodiment include, but are not limited to:

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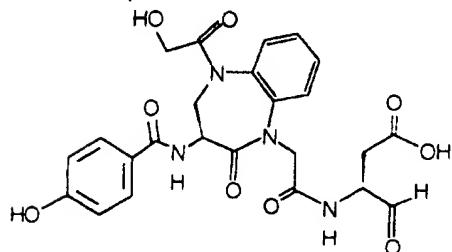
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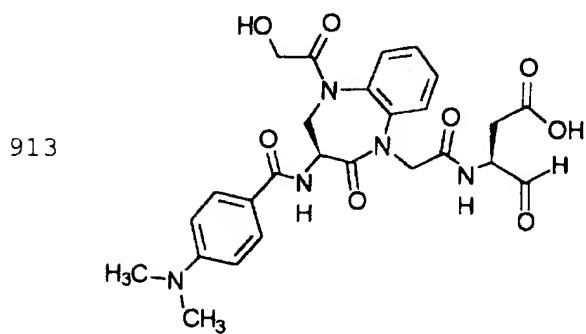
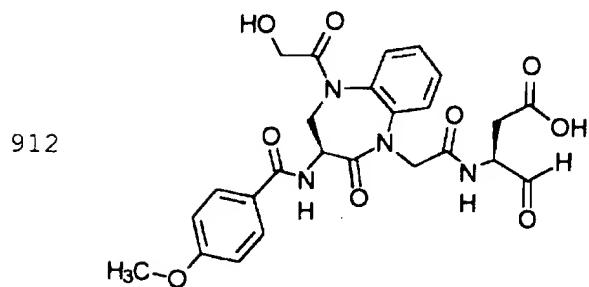
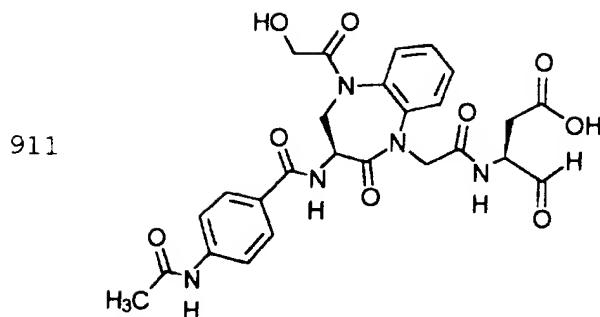
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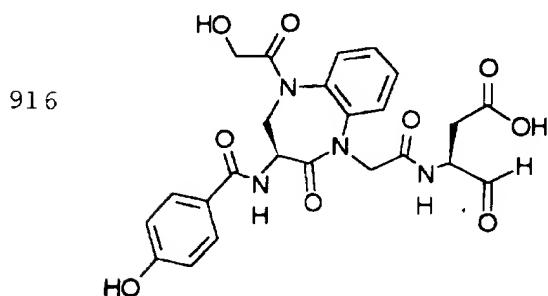


;

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; and



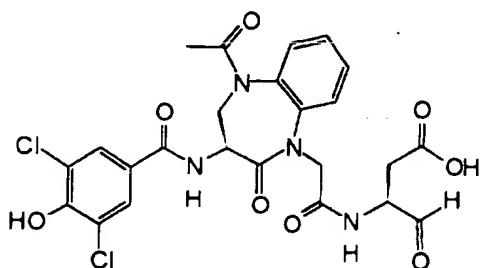
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Most preferably, Ar₃ is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R₅, -N(R₉)(R₁₀), or -O-R₅.

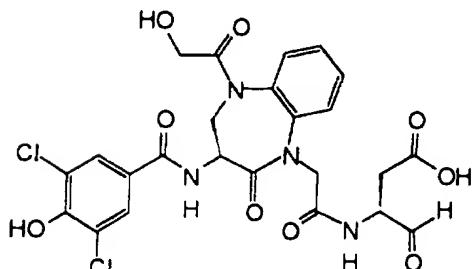
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Preferred compounds of this most preferred embodiment include, but are not limited to:

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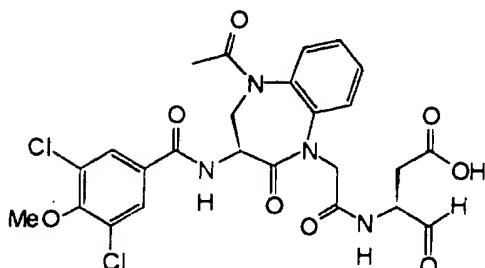


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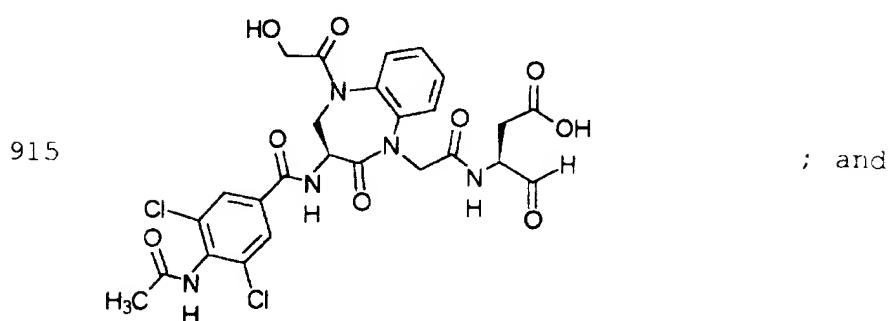
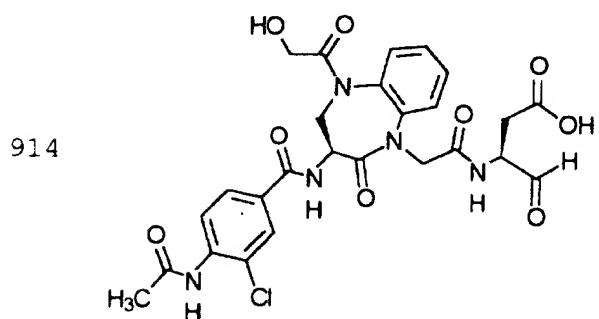
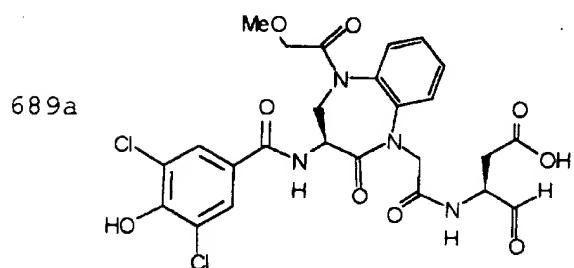
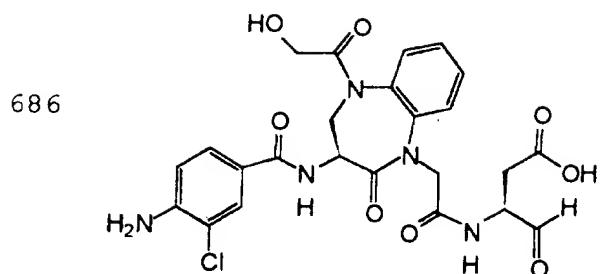


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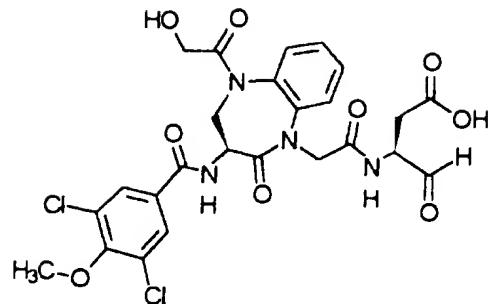


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- 249 -

918

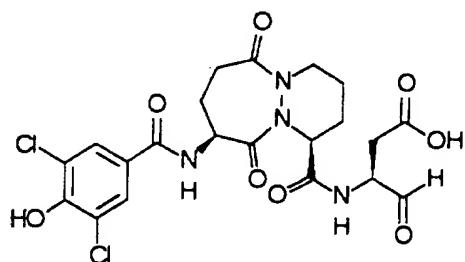


Other preferred compounds of
this most preferred embodiment include, but are not
limited to:

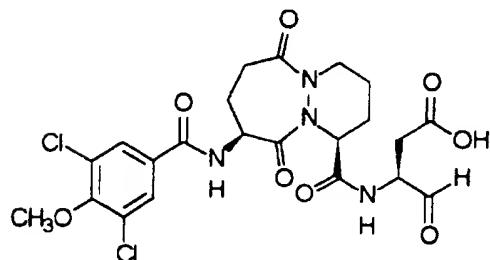
5

214k

; and



214m

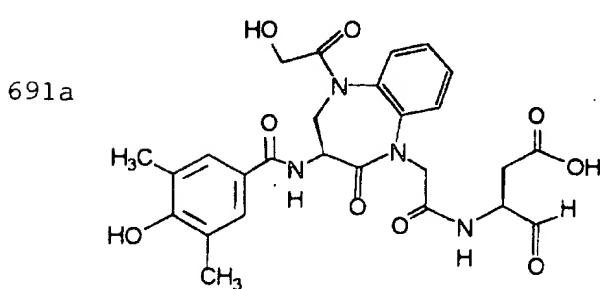
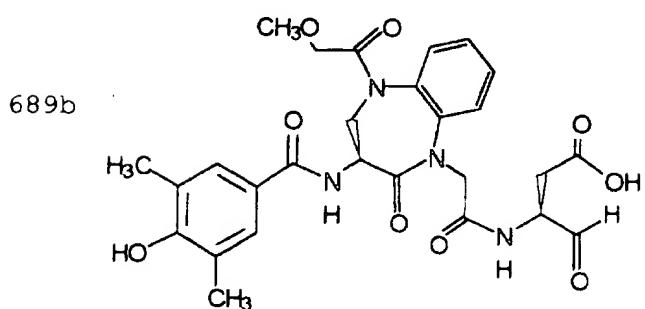
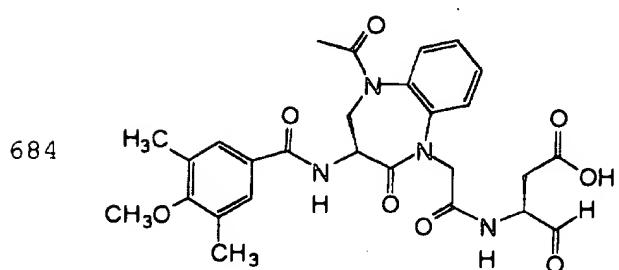
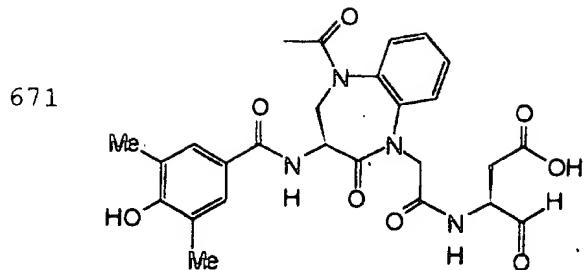


10

Alternatively, Ar₃ is phenyl being
singly or multiply substituted at the 3- or 5-position
by -R₉, wherein R₉ is a C₁₋₄ straight or branched alkyl
group; and at the 4-position by -O-R₅.

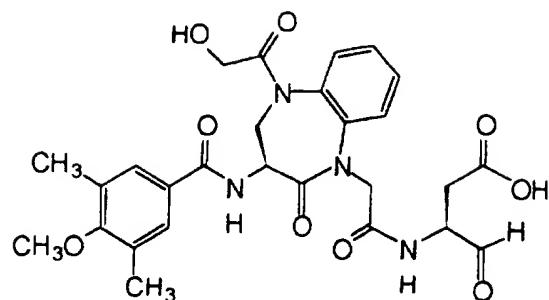
Preferred compounds of this
most preferred embodiment include, but are not limited
to:

- 250 -



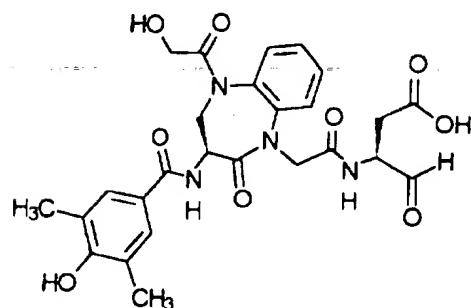
- 251 -

694



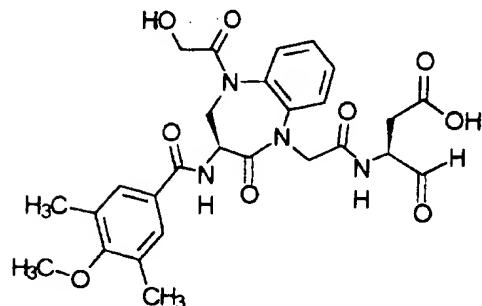
;

917



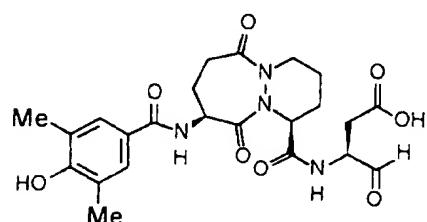
; and

922



Another preferred compound of
5 this most preferred embodiment includes, but is not
limited to:

214w



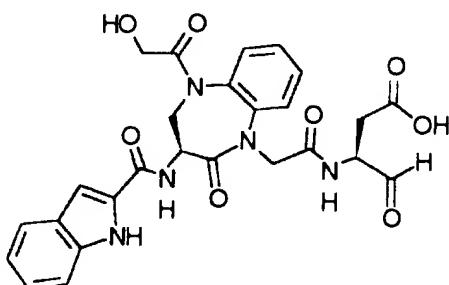
- 252 -

Alternatively, in this more preferred embodiment:

R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃ cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q₁.

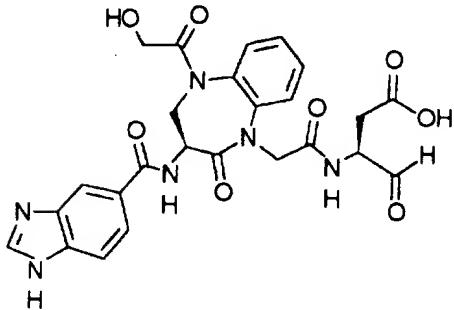
Preferred compounds of this more preferred embodiment include, but are not limited to:

919



; and

920



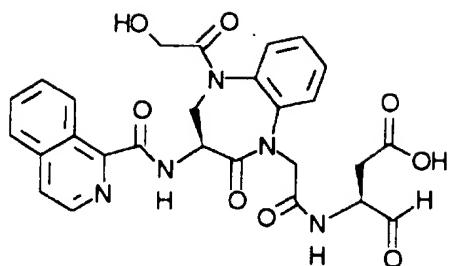
Most preferably, the Ar₃ cyclic group is isoquinolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁.

A preferred compound of this most preferred embodiment includes, but is not limited

- 253 -

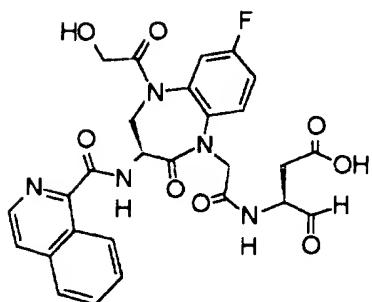
to:

696



;

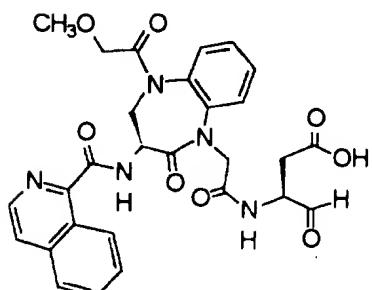
696-1



; and

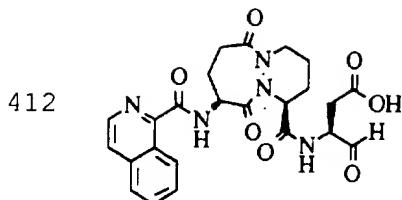
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699



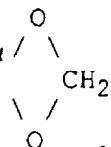
Another preferred compound of
this most preferred embodiment includes, but is not
limited to:

- 254 -



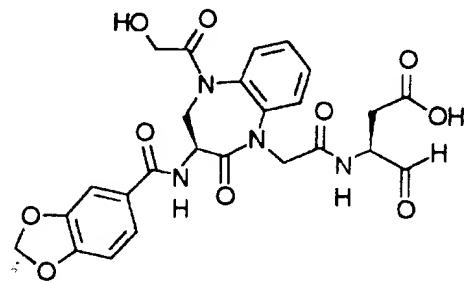
Alternatively, in this more preferred embodiment R₅ is -C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic group is phenyl, substituted by

10



A preferred compound of this more preferred embodiment includes, but is not limited to:

910

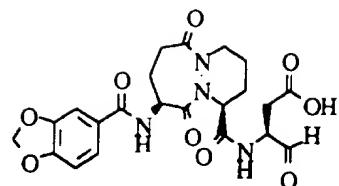


15

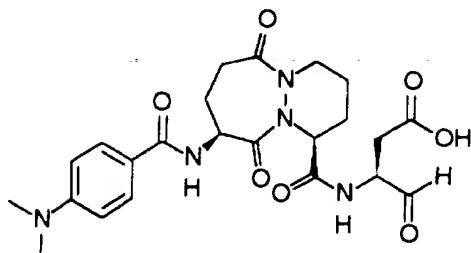
A preferred compound of this more preferred embodiment includes, but is not limited to:

- 255 -

415

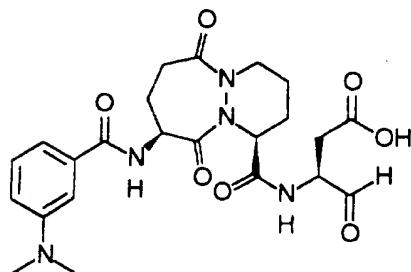


214f

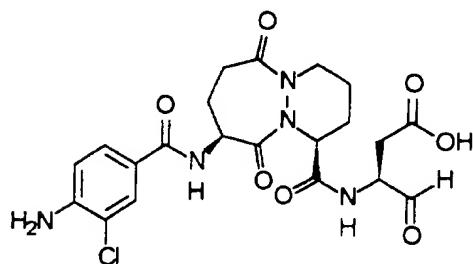


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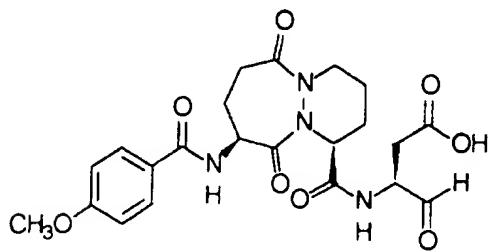
214g



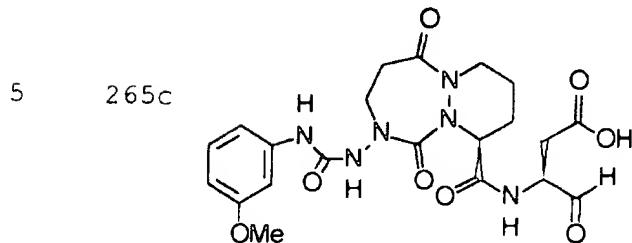
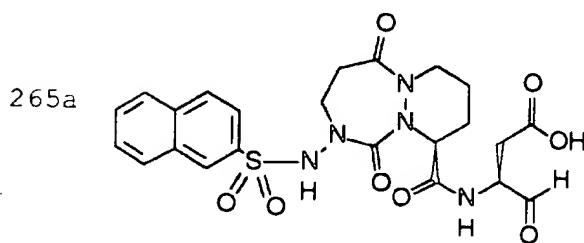
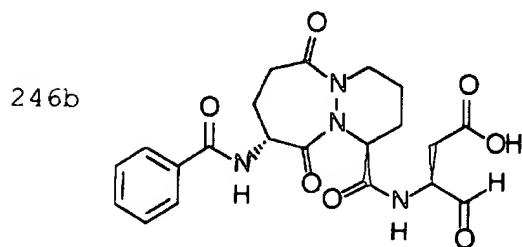
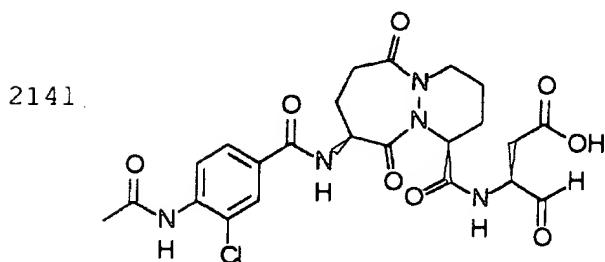
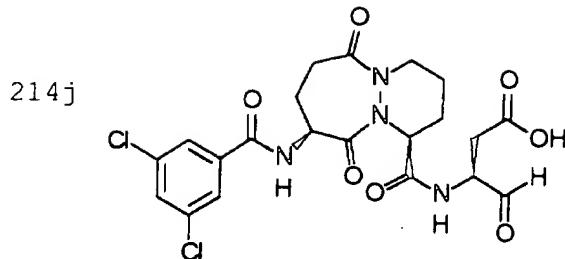
214h



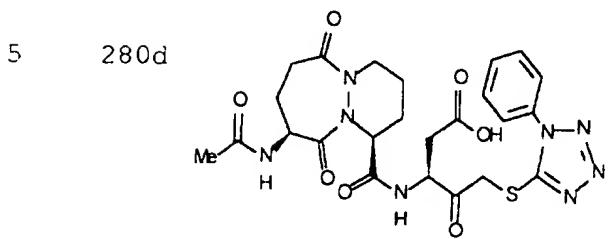
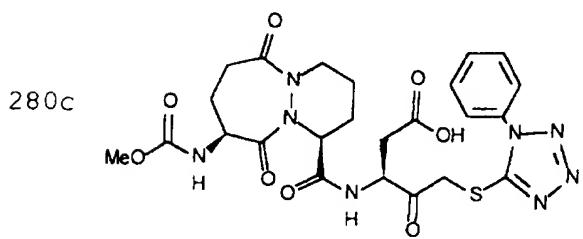
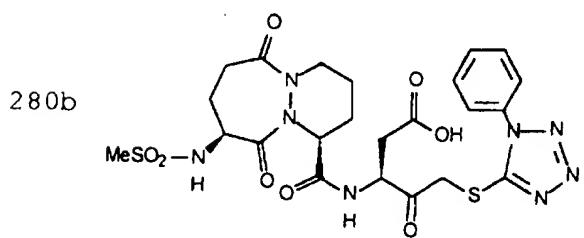
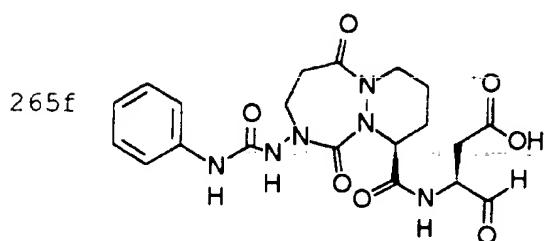
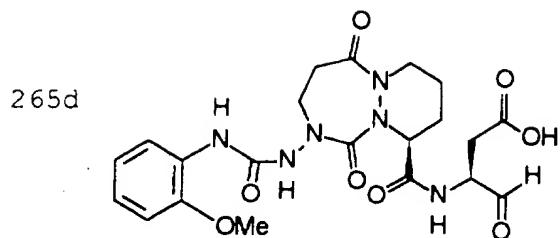
214i



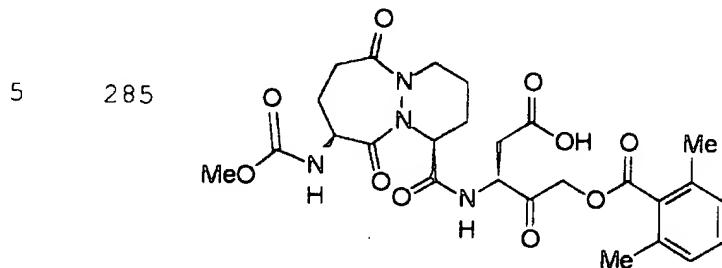
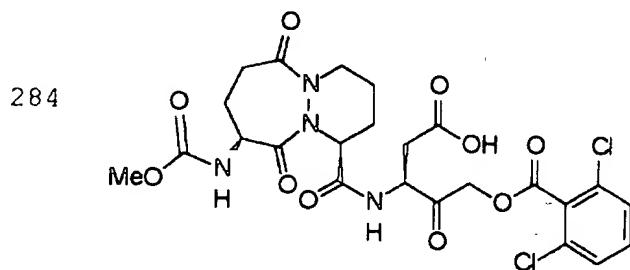
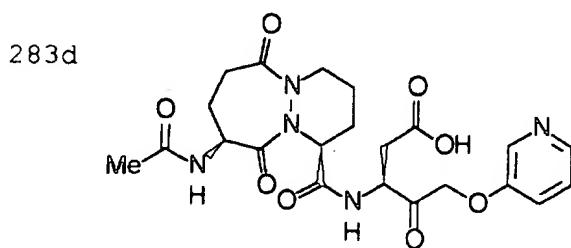
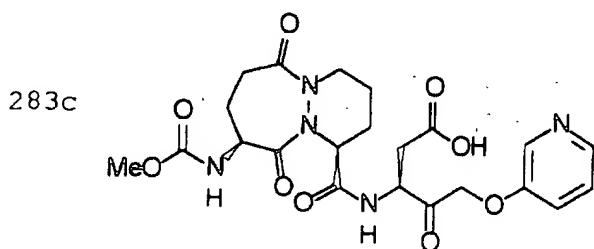
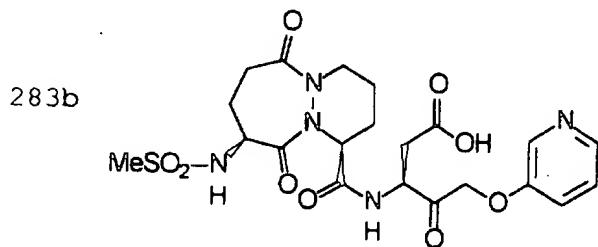
- 256 -



- 257 -

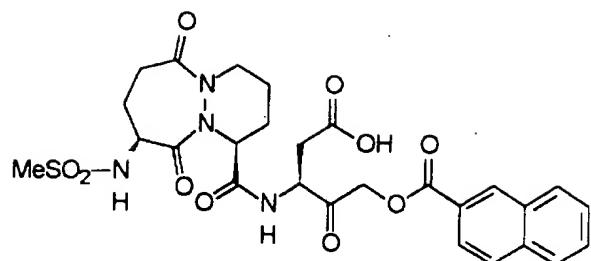


- 258 -

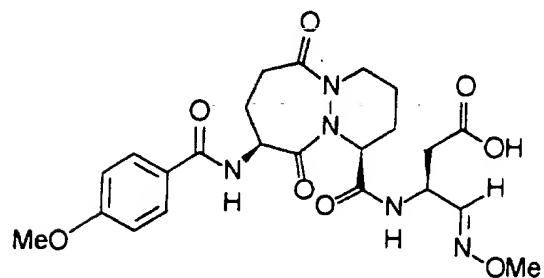


- 259 -

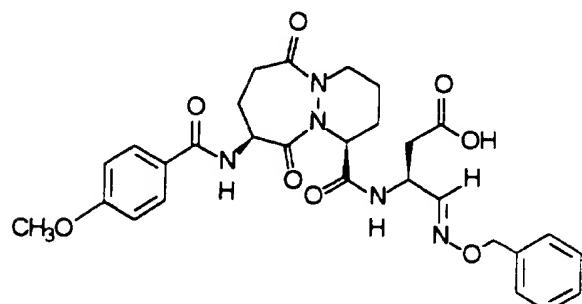
286



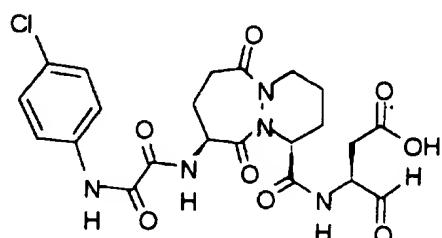
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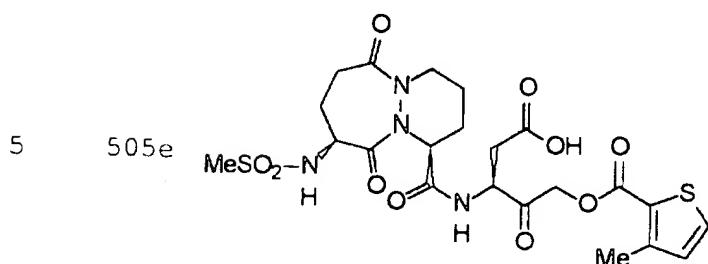
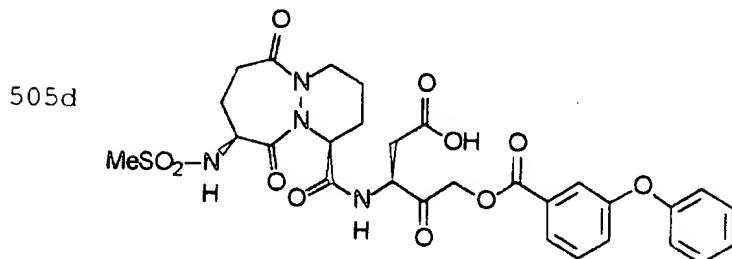
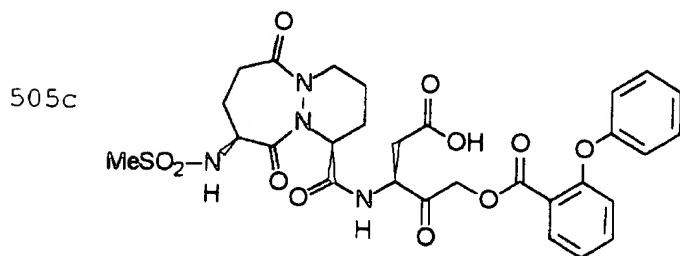
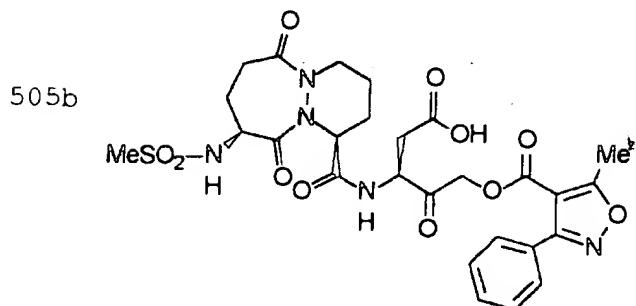
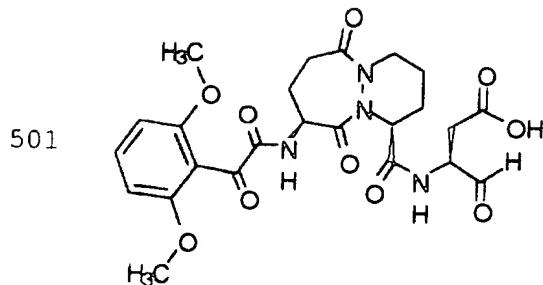
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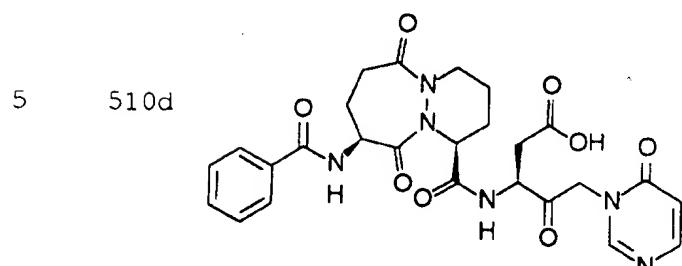
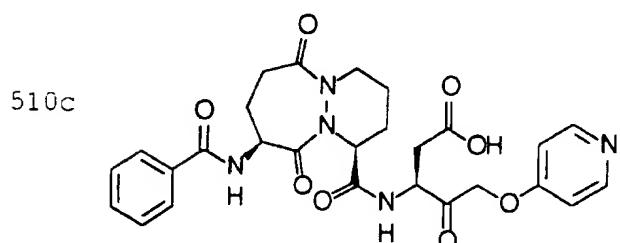
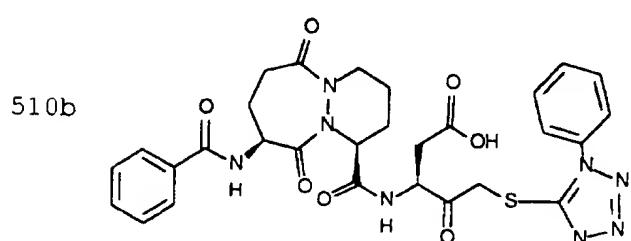
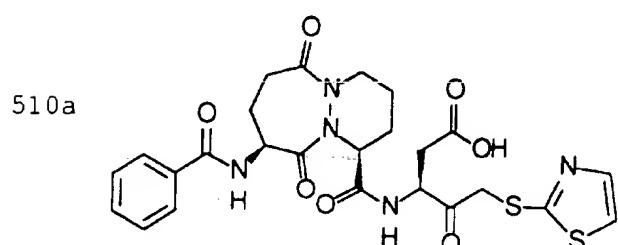
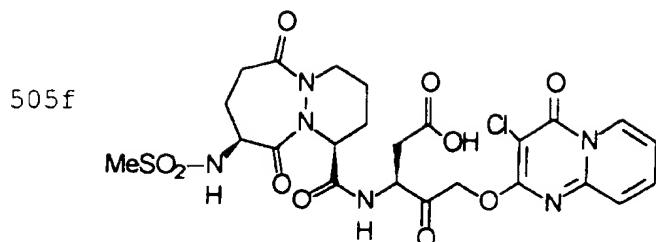
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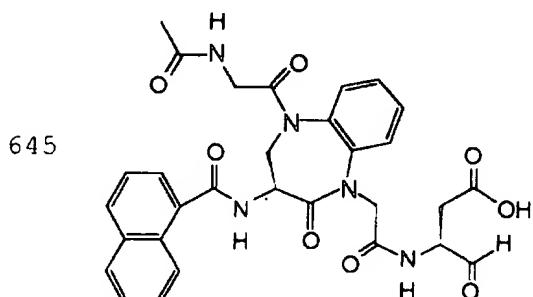
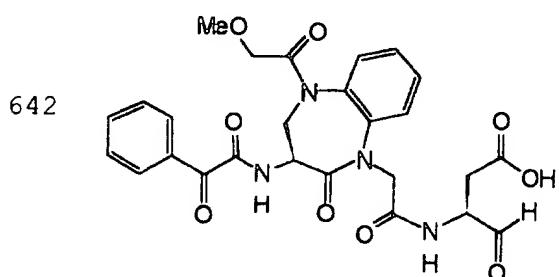
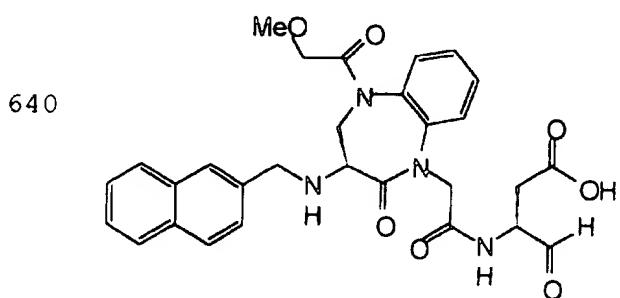
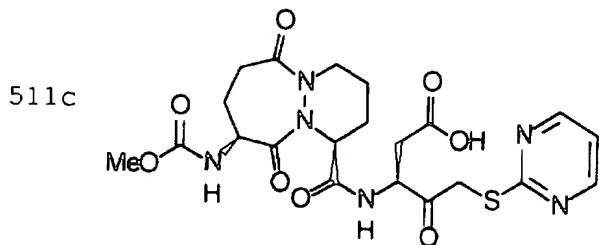
- 260 -



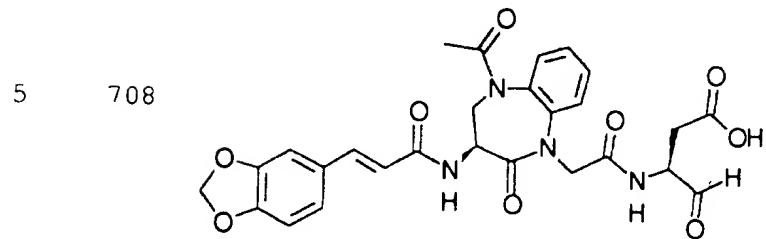
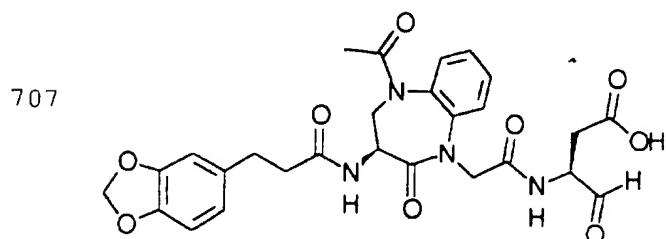
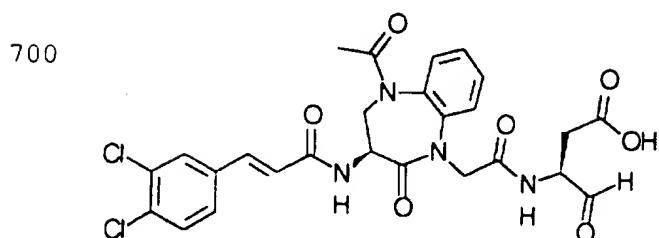
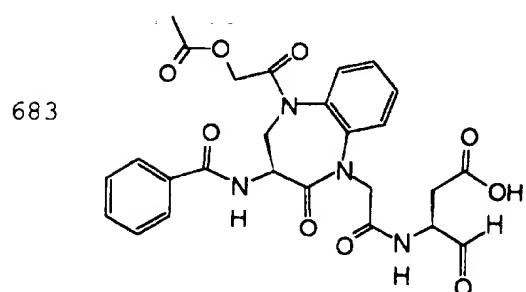
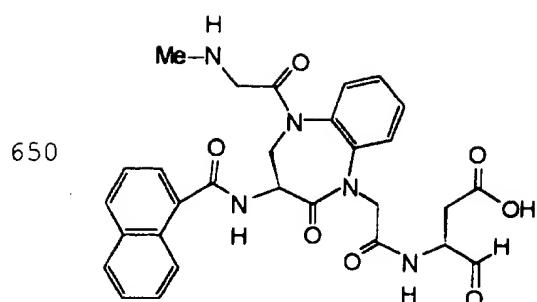
- 261 -



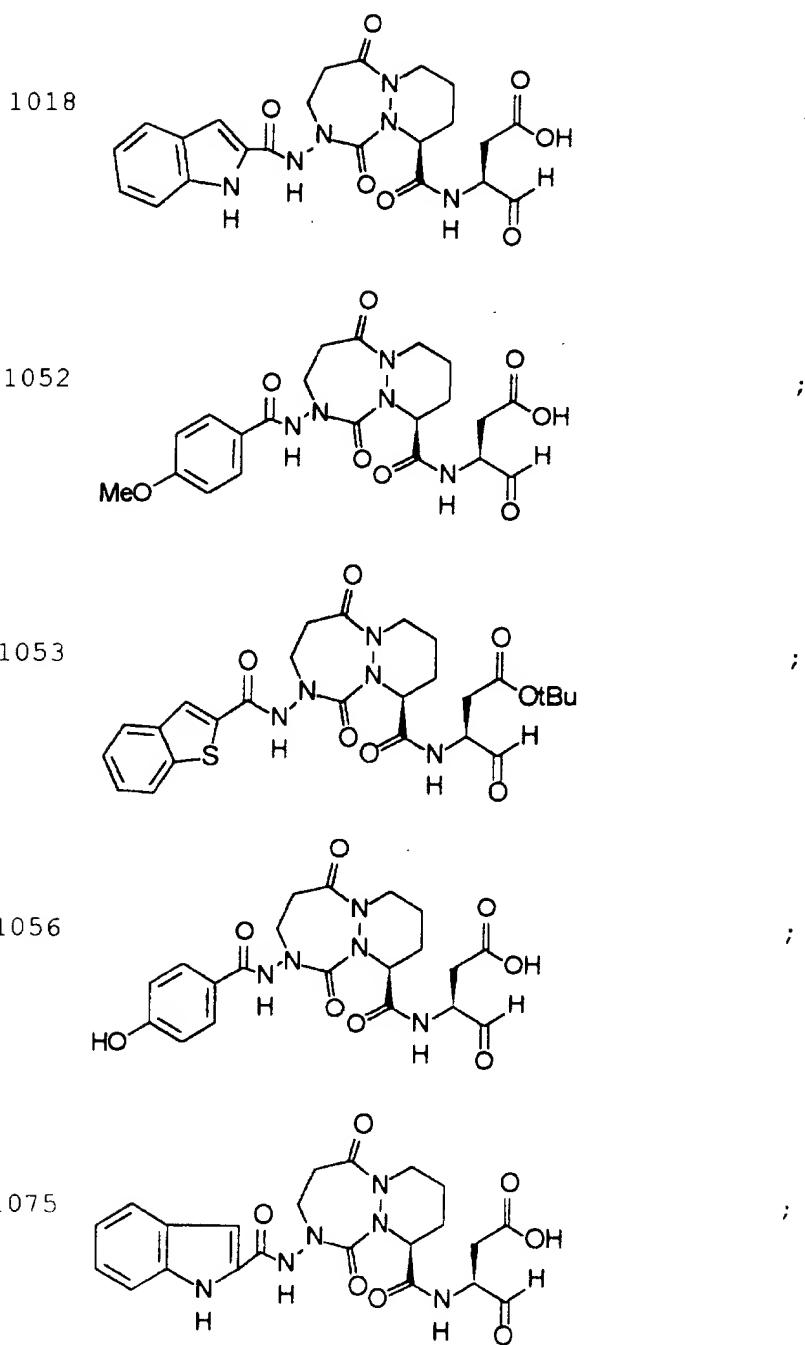
- 262 -



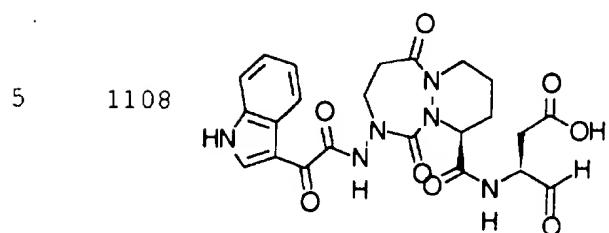
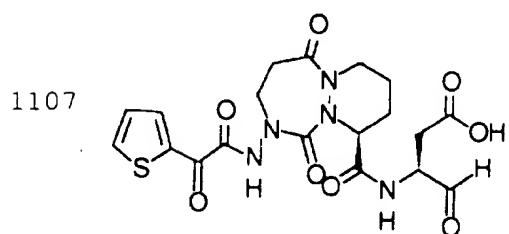
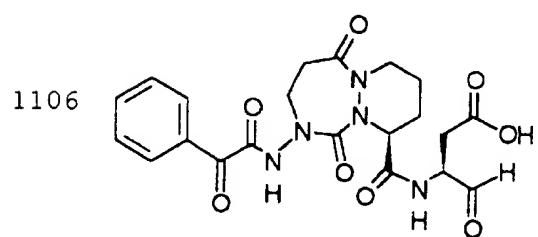
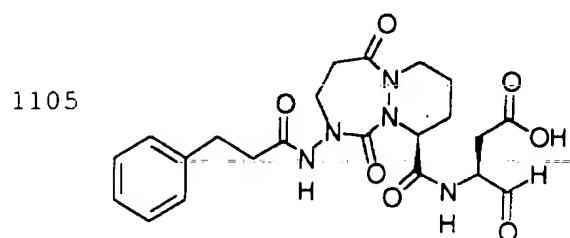
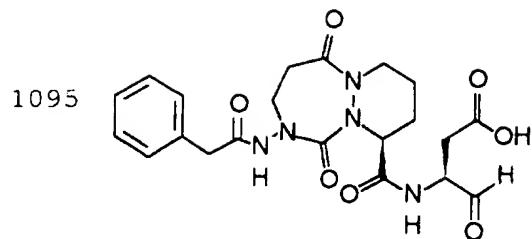
- 263 -



- 264 -

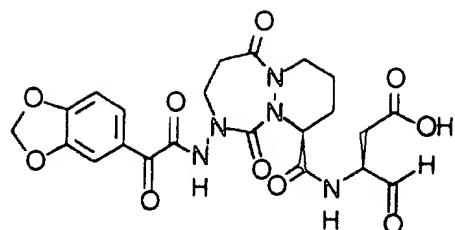


- 265 -

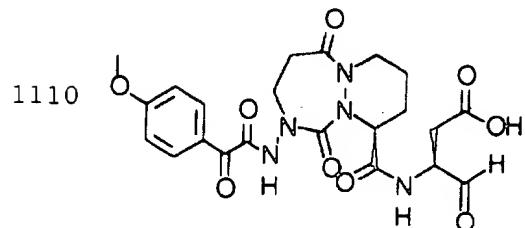


- 266 -

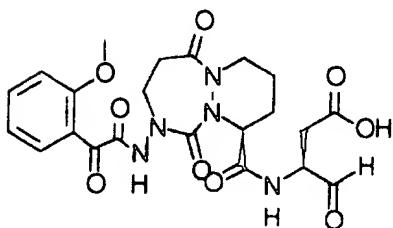
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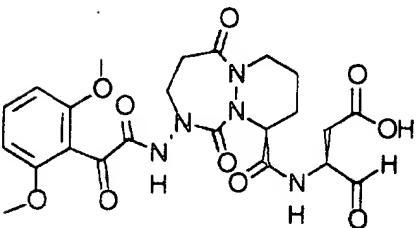
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1111

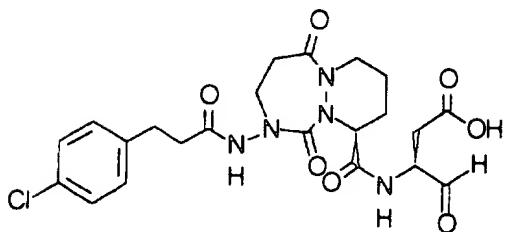


1112

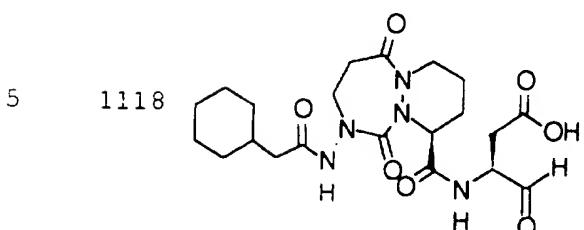
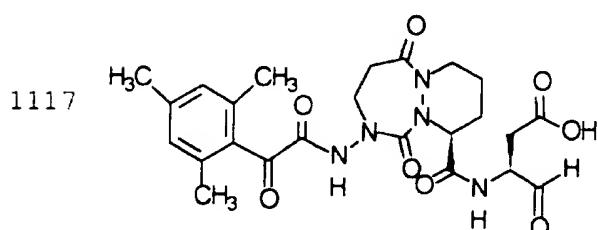
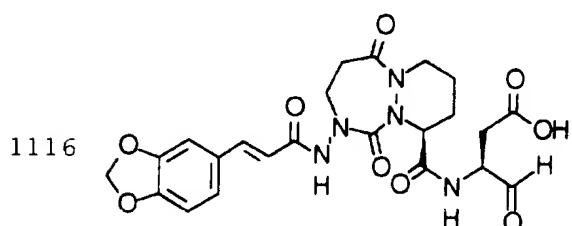
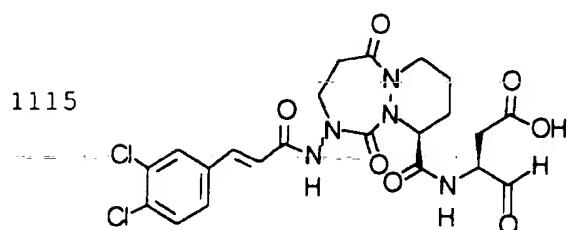
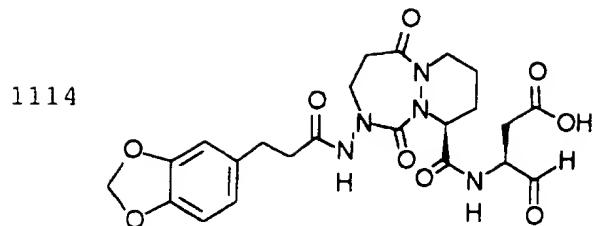


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1113

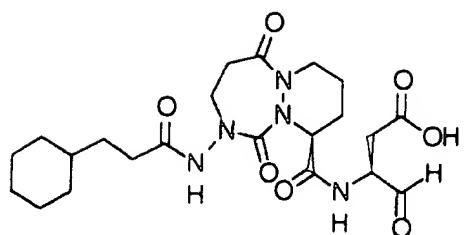


- 267 -

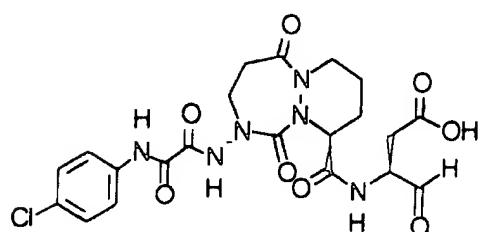


- 268 -

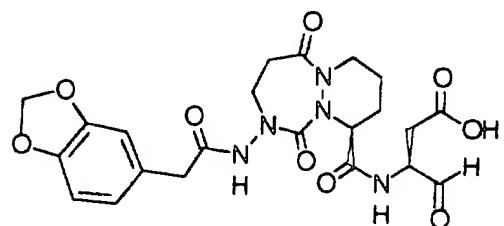
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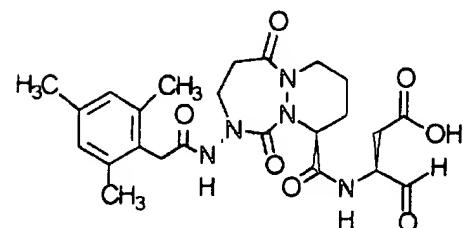
1120



1121

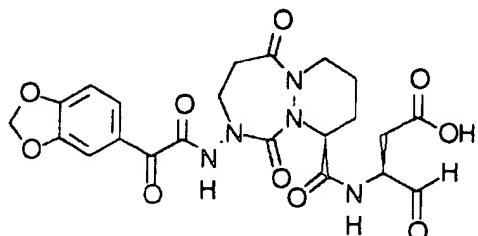


1122



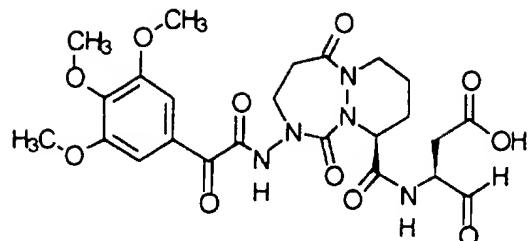
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1123

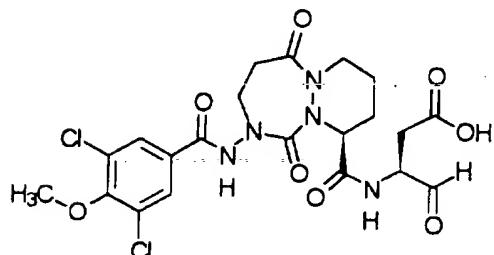


- 269 -

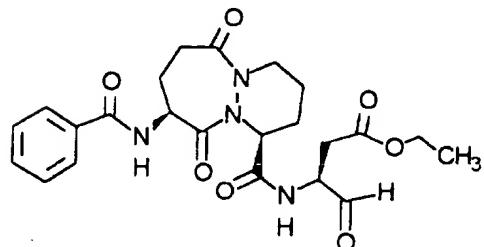
1124



1125

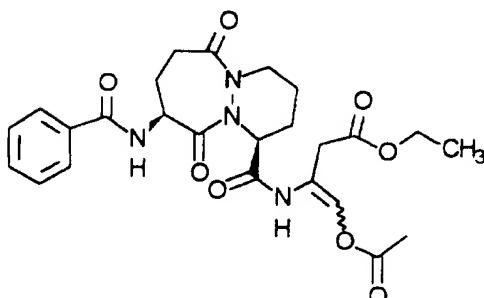


2100i



5

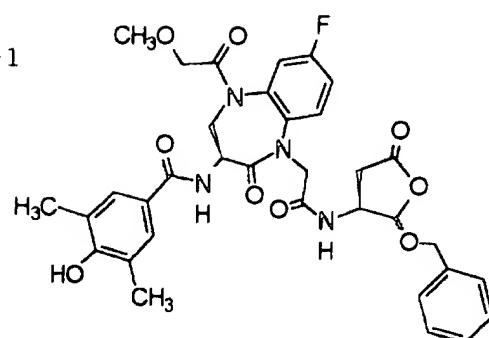
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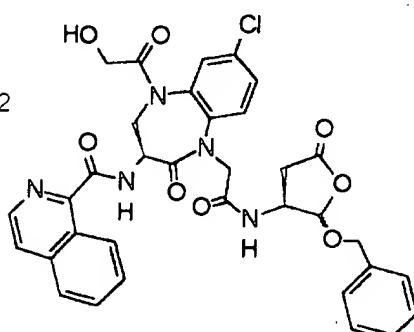
Other compounds of embodiment (K) include,
but are not limited to:

- 270 -

688b-1

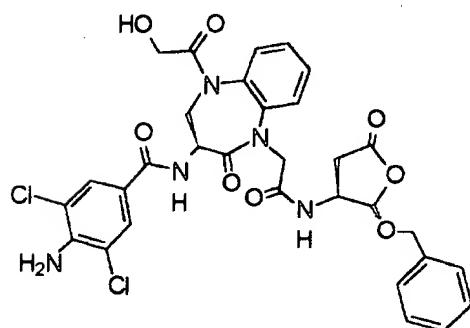


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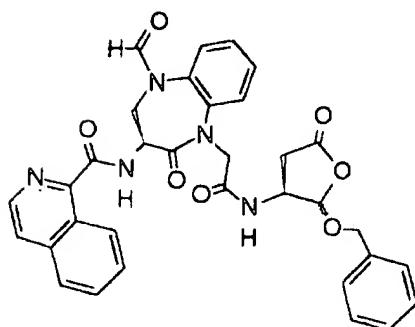


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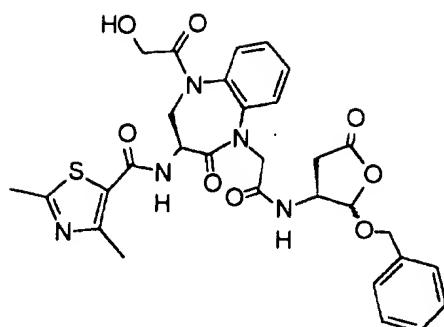


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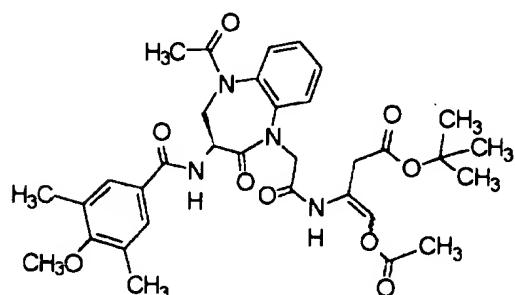
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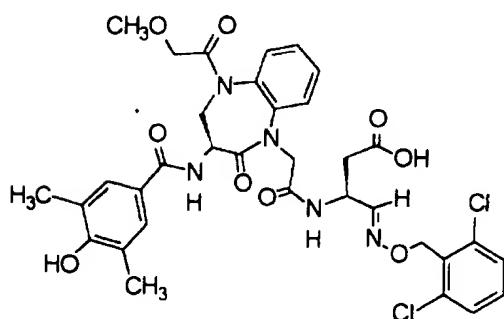


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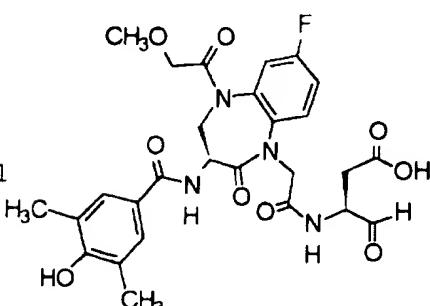
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688c



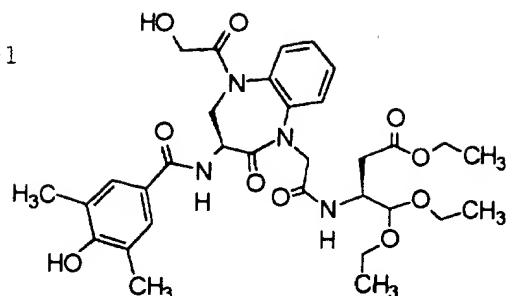
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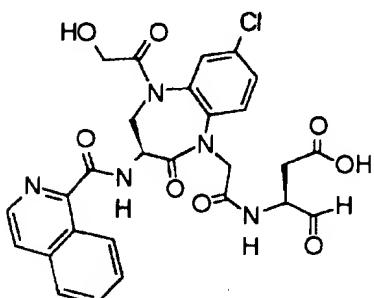
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- 272 -

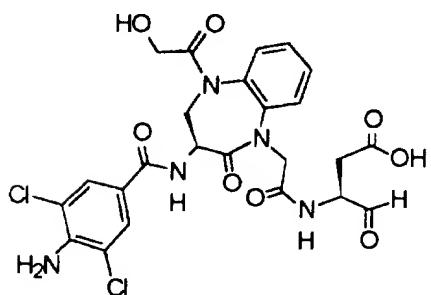
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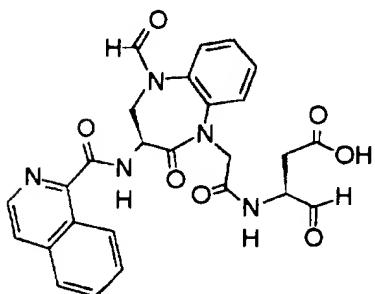
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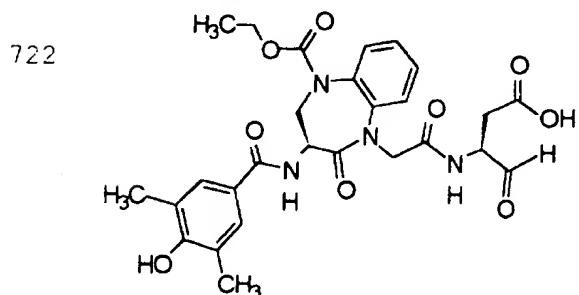
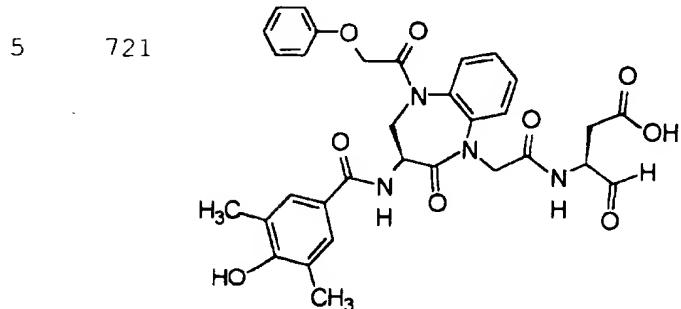
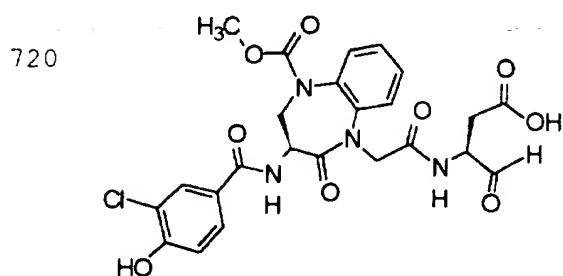
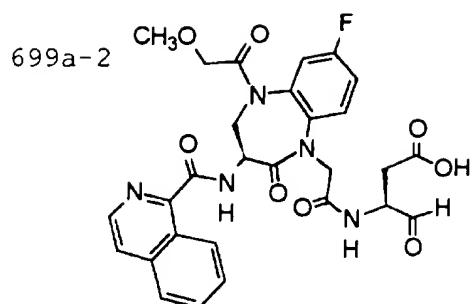
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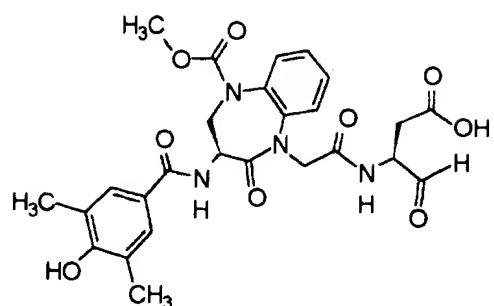


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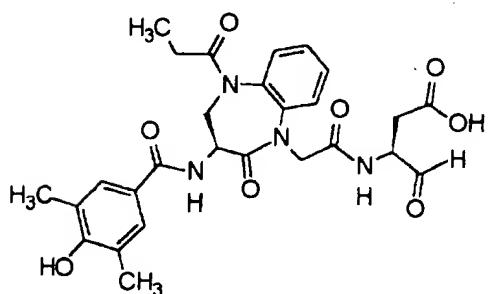


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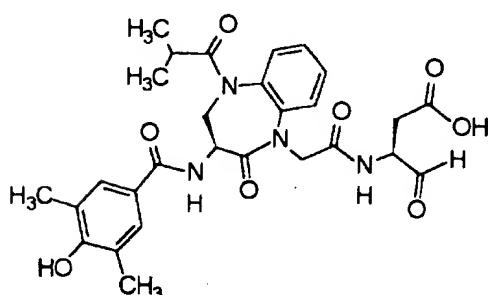
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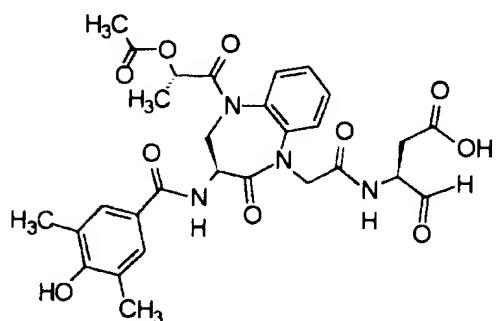
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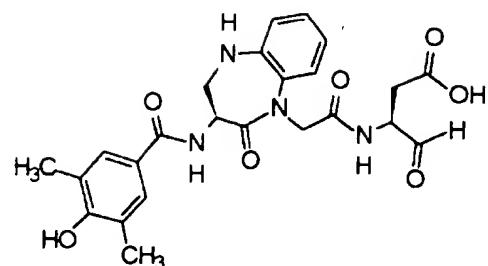


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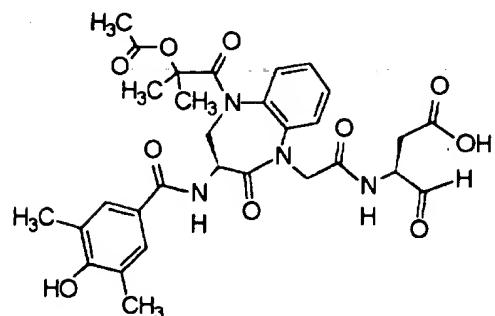


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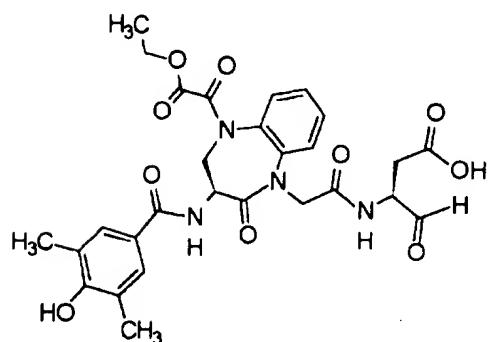


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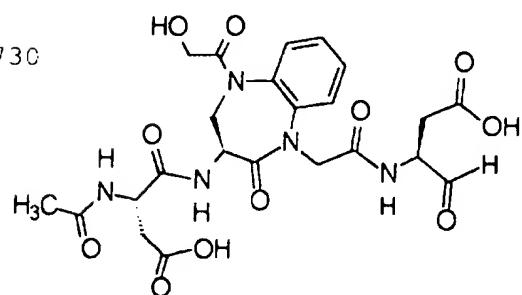


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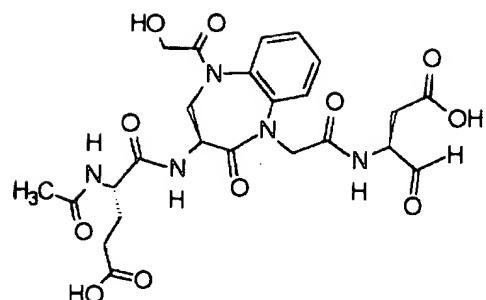


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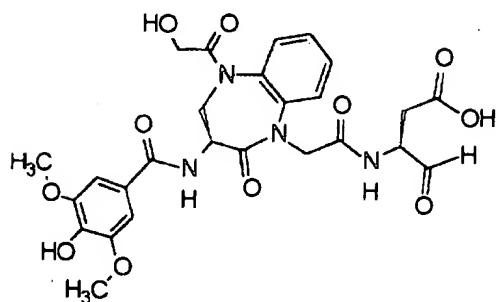


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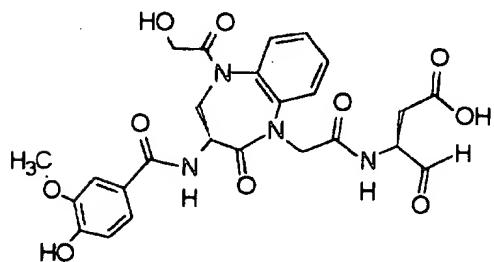


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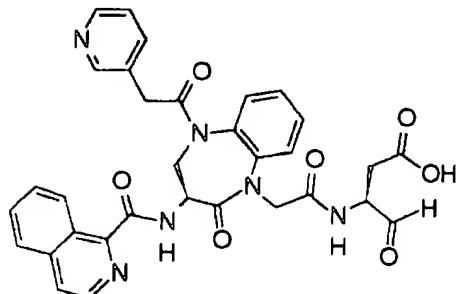


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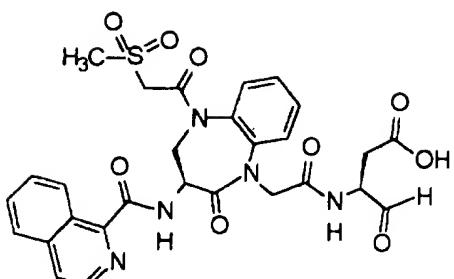


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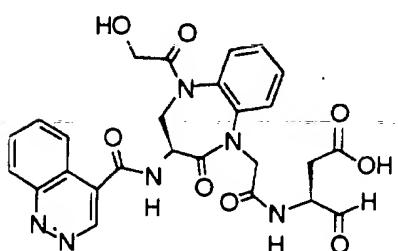


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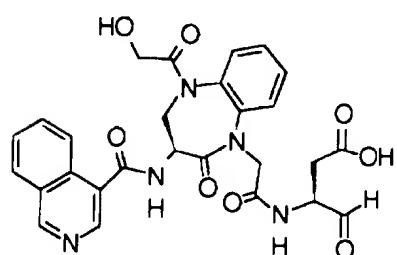


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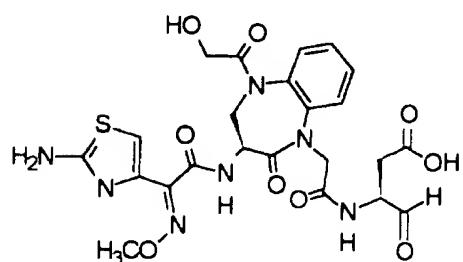


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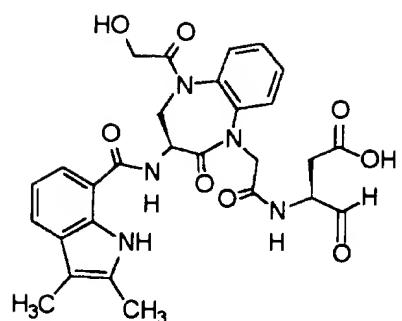


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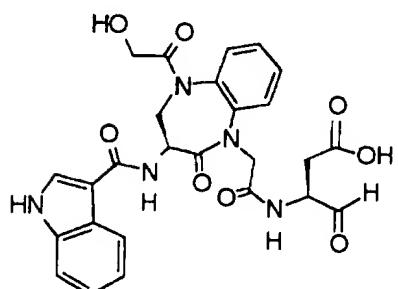


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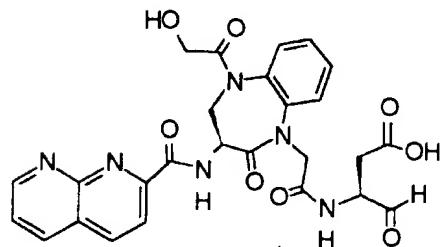
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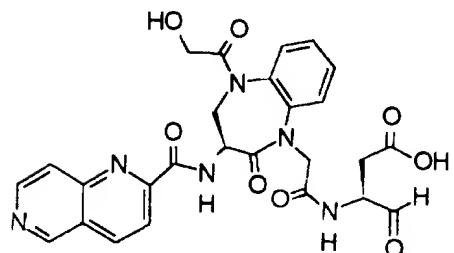
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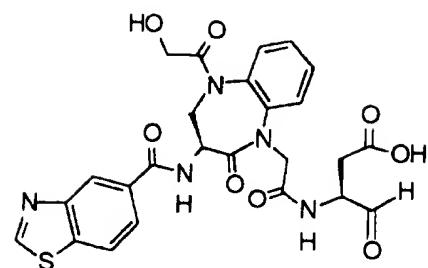


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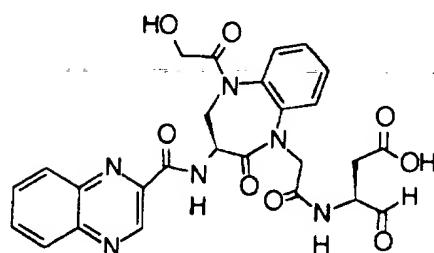


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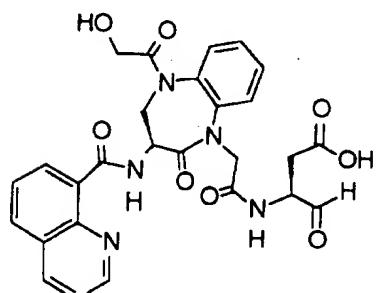


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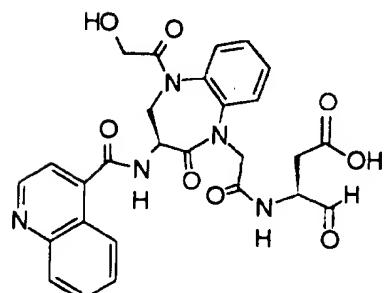


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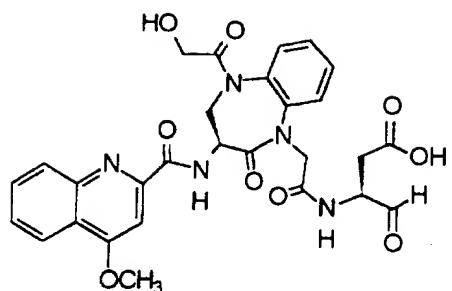


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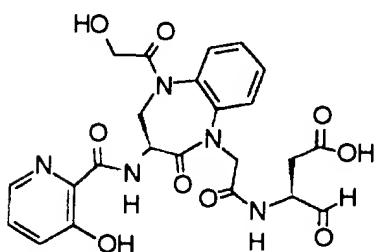


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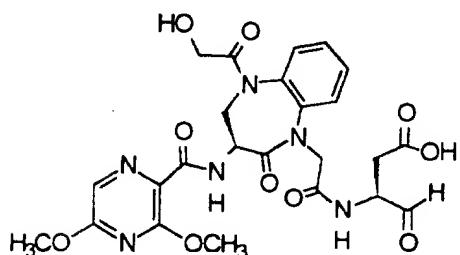
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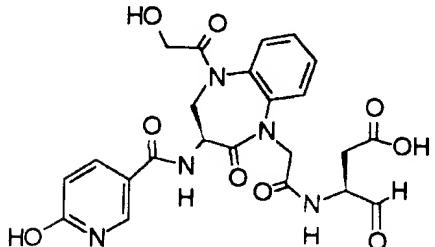
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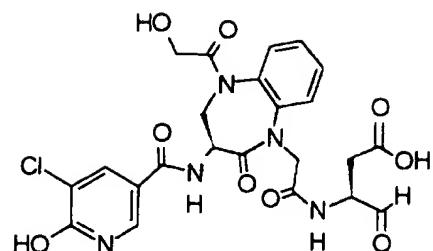


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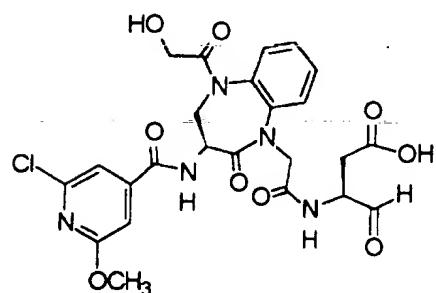


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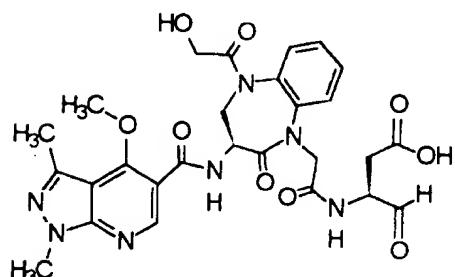
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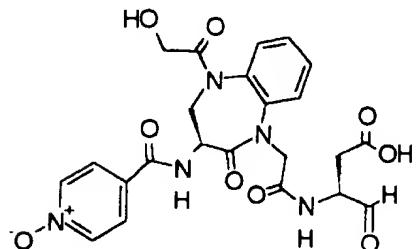
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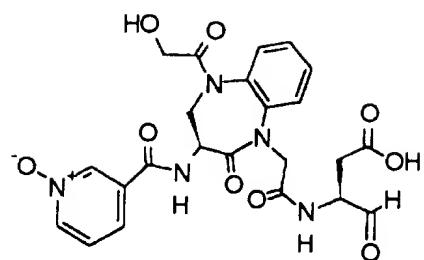


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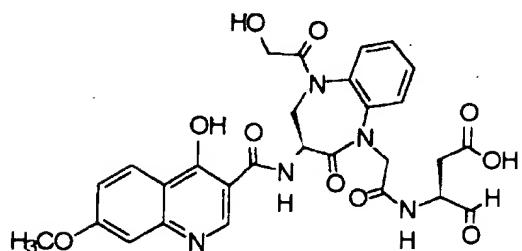


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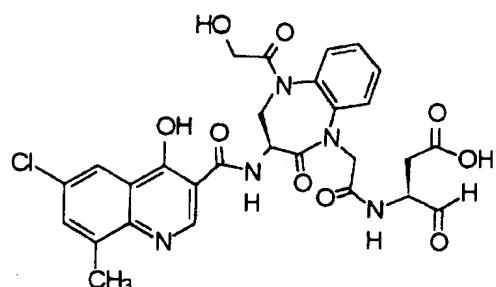


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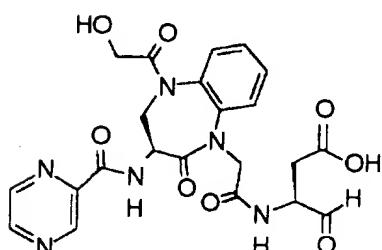


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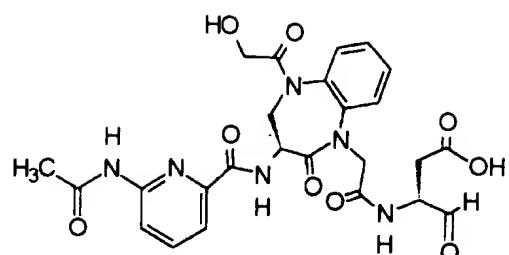


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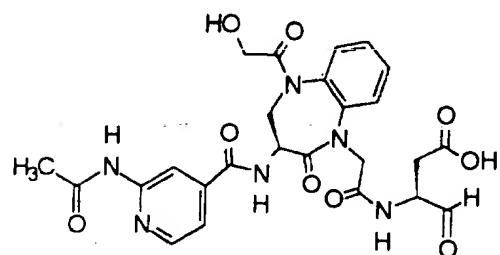


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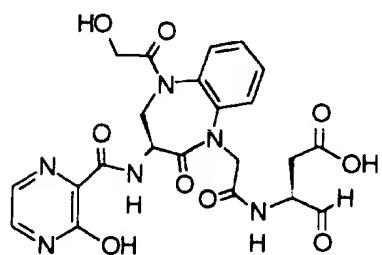
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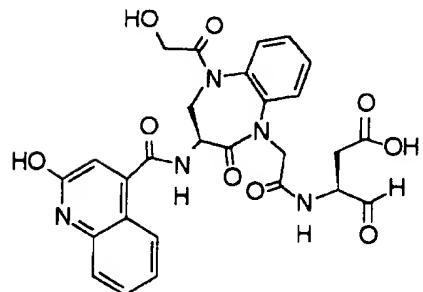
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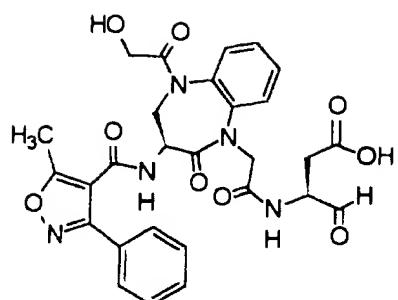


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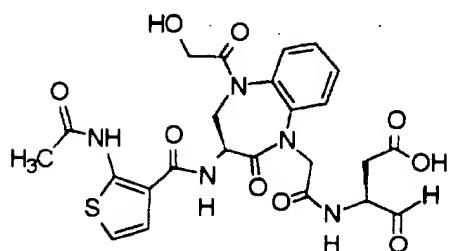


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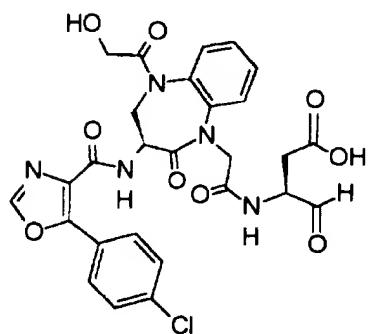


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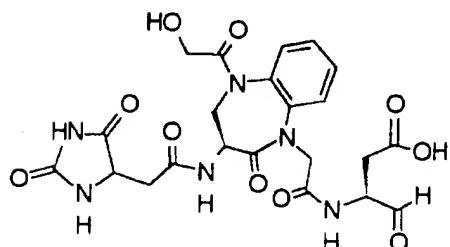


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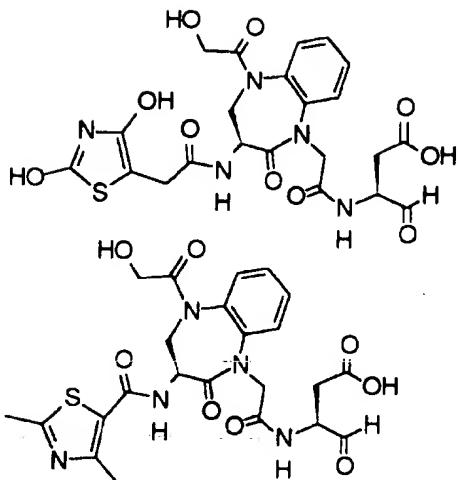


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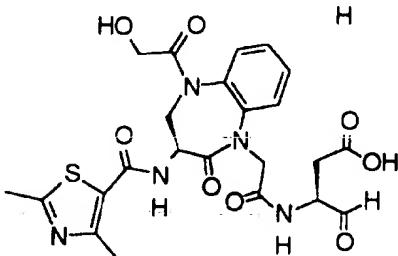
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767



; and

801



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The most preferred compounds of embodiments (K) and (L) are those wherein the Ar₃ cyclic group is isoquinolyl.

Compounds of this invention are described in co-pending United States Application Serial Nos.

10

08/575,641 and 08/598,332 the disclosures of which are herein incorporated by reference.

15

The compounds of this invention have a molecular weight of less than or equal to about 700 Daltons, and more preferably between about 400 and 600 Daltons. These preferred compounds may be readily absorbed by the bloodstream of patients upon oral administration. This oral availability makes such compounds excellent agents for orally-administered treatment and prevention regimens against IL-1-, apoptosis-, IGIF- or IFN- γ mediated diseases.

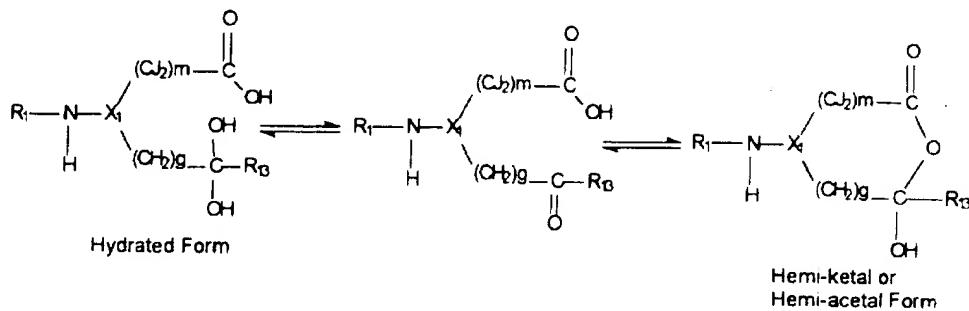
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It should be understood that the compounds of this invention may exist in various equilibrium forms, depending on conditions including choice of solvent, pH, and others known to the practitioner skilled in the art. All such forms of these compounds are expressly included in the present invention. In particular, many

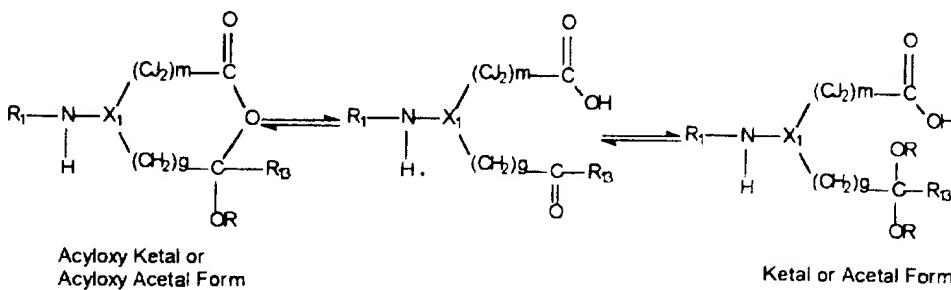
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of the compounds of this invention, especially those which contain aldehyde or ketone groups in R₃ and carboxylic acid groups in T, may take hemi-ketal (or hemi-acetal) or hydrated forms. For example, compounds 5 of embodiment (A) may take the forms depicted below:

EQ1



Depending on the choice of solvent and other conditions known to the practitioner skilled in the art, compounds of this invention may also take acyloxy ketal, acyloxy acetal, ketal or acetal form:
10



In addition, it should be understood that the equilibrium forms of the compounds of this invention may include tautomeric forms. All such forms of these compounds are expressly included in the present 15 invention.

It should be understood that the compounds of this invention may be modified by appropriate

functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. In addition, the compounds may be altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or other biochemical processes on the pro-drug. Such pro-drug forms typically demonstrate little or no activity in *in vitro* assays. Some examples of pro-drug forms include ketal, acetal, oxime, imine, and hydrazone forms of compounds which contain ketone or aldehyde groups, especially where they occur in the R₃ group of the compounds of this invention. Other examples of pro-drug forms include the hemi-ketal, hemi-acetal, acyloxy ketal, acyloxy acetal, ketal, and acetal forms that are described in EQ1 and EQ2.

ICE and TX Cleave and Thereby Activate Pro-IGIF

The ICE protease was identified previously by virtue of its ability to process inactive pro-IL-1 β to mature active IL-1 β , a pro-inflammatory molecule, in vitro and in vivo. Here we show that ICE and its close homologue TX (Caspase-4, C. Faucheu et al., EMBOJ, 14, p. 1914 (1995)) can proteolytically cleave inactive pro-IGIF. This processing step is required to convert pro-IGIF to its active mature form, IGIF. Cleavage of pro-IGIF by ICE, and presumably by TX, also facilitates the export of IGIF out of cells.

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We first used transient co-expression of plasmids transfected into Cos cells to determine whether any known members of the ICE/CED-3 protease family can process pro-IGIF to IGIF in cultured cells
5 (Example 23) (Fig. 1A).

Fig. 1A demonstrates that ICE cleaves pro-IGIF in Cos cells co-transfected with plasmids that express pro-IGIF in the presence of active ICE. Cos cells were transfected with an expression plasmid for
10 pro-IGIF alone (lane 2) or in combination with the indicated expression plasmids encoding wild type or inactive mutants of ICE/CED-3 family of proteases (lanes 3-12). Cell lysates were prepared and analyzed for the presence of IGIF protein by immunoblotting with
15 an anti-IGIF antiserum. Lane 1 contained lysates from mock transfected cells.

Co-expression of pro-IGIF with ICE or TX resulted in the cleavage of pro-IGIF into a polypeptide similar in size to the naturally-occurring 18-kDa mature IGIF. This processing event is blocked by single point mutations that alter the catalytic cysteine residues and thus inactivate ICE and TX (Y. Gu et al., EMBO, 14, p. 1923 (1995)).

Co-expression with CPP32 (Caspase-3), a
25 protease involved in programmed cell death (T. Fernandes-Alnemri et al., J. Biol. Chem., 269, p. 30761 (1994); D. W. Nicholson et al., Nature, 376, p. 37 (1995)), resulted in the cleavage of pro-IGIF into a smaller polypeptide, while co-expression with CMH-1
30 (Caspase-7), a close homolog of CPP32 (J. A. Lippke et al., J. Biol. Chem., 271, p. 1825 (1996)), failed to cleave pro-IGIF to any significant extent. Thus, ICE and TX appear to be capable of cleaving pro-IGIF into a

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polypeptide similar in size to the naturally-occurring 18-kDa IGIF.

We next examined the ability of these cysteine proteases to cleave pro-IGIF in vitro using a purified, recombinant (His)₆-tagged pro-IGIF as a substrate (**Example 23**).

Fig. 1B demonstrates that pro-IGIF is cleaved in vitro by ICE. Purified recombinant (His)₆-tagged pro-IGIF (2 µg) was incubated with the indicated cysteine protease in the presence or absence of ICE or CPP32 inhibitors as described in **Example 23**. The cleavage products were analyzed by SDS-PAGE and Coomassie Blue staining.

ICE cleaved the 24 kDa pro-IGIF into two polypeptides of approximately 18-kDa and 6-kDa. N-terminal amino acid sequencing of the ICE cleavage products indicated that the 18-kDa polypeptide contains the same N-terminal amino acid residues (Asn-Phe-Gly-Arg-Leu) as the naturally occurring IGIF.

This shows that ICE cleaves pro-IGIF at the authentic processing site (Asp35-Asn36) (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995)). N-terminal amino acid sequencing of the CPP32 cleavage products indicated that CPP32 cleaved pro-IGIF at Asp69-Ile70.

The cleavage by ICE of pro-IGIF is highly specific with a catalytic efficiency (k_{cat}/K_M) of $1.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ ($K_M = 0.6 \pm 0.1 \mu\text{M}$; $k_{cat} = 8.6 \pm 0.3 \text{ s}^{-1}$) and is inhibited by specific ICE inhibitors (Ac-Tyr-Val-Ala-Asp-aldehyde) and Cbz-Val-Ala-Asp-(2,6-dichlorobenzoyl)oxy)methylketone, (N.A. Thornberry et al., Nature, 356, p. 768 (1992); R. E. Dolle et al., J. Med. Chem., 37, p. 563 (1994)).

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Fig. 1C demonstrates that ICE cleavage in vitro activates pro-IGIF. Uncleaved pro-IGIF, ICE- or CPP32-cleaved products of pro-IGIF, or recombinant mature IGIF (rIGIF) were each added to A.E7 cell cultures to a final concentration of 12 ng/ml or 120 ng/ml (see, Example 23). Eighteen hours later, IFN- γ in the cultural medium was quantified by ELISA. While the uncleaved pro-IGIF had no detectable IFN- γ inducing activity, ICE-cleaved pro-IGIF was active in inducing IFN- γ production in Th1 cells.

Like ICE, the ICE homolog TX also cleaved pro-IGIF into similarly sized polypeptides. However, its catalytic efficiency was about two orders of magnitude lower than that shown for ICE.

Consistent with the observations from the Cos cell experiments above, CPP32 cleaved pro-IGIF at a different site (Asp69-Ile70) and the resulting polypeptides had little IFN- γ inducing activity (Fig. 1C). CMH-1 and granzyme B each failed to cleave pro-IGIF to any significant extent.

Together, these results demonstrate that, both in Cos cells and in vitro, ICE and TX are capable of processing the inactive pro-IGIF precursor at the authentic maturation site to generate a biologically active IGIF molecule.

Processing of Pro-IGIF by ICE Facilitates Its Export

IGIF is produced by activated Kupffer cells and macrophages in vivo and is exported out of the cells upon stimulation by endotoxin (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995)). We used the Cos cell co-expression system (Example 23) to examine

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whether the intracellular cleavage of pro-IGIF by ICE would facilitate the export of mature IGIF from the cell. Such is the case for pro-IL-1 β when it is cleaved by ICE into active IL-1 β (N.A. Thornberry et al., *Nature*, 356, p. 768 (1992)).

In **Fig. 2A**, Cos cells transfected with an expression plasmid for pro-IGIF alone (lanes 2 and 6) or in combination with an expression plasmid encoding wild type (lanes 3 and 7) or inactive mutant ICE (lanes 4 and 8) were metabolically labeled with 35 S-methionine (see, **Example 24**). Cell lysates (left) and conditioned medium (right) were immunoprecipitated with an anti-IGIF antiserum. The immunoprecipitated proteins were analyzed by SDS-PAGE and fluorography (**Fig. 2A**).

An 18-kDa polypeptide corresponding in size to mature IGIF was detected in the conditioned medium of Cos cells co-expressing pro-IGIF and ICE, while Cos cells co-expressing pro-IGIF and an inactive ICE mutant (ICE-C285S), or pro-IGIF alone (-) exported only very low levels of pro-IGIF and no detectable mature IGIF. We estimate that about 10% of the mature IGIF was exported from co-transfected cells, while greater than 99% of pro-IGIF was retained within the cells.

We also measured the presence of IFN- γ inducing activity in cell lysates and in the conditioned medium of the above transfected cells (see, **Example 24**). IFN- γ inducing activity was detected in both cell lysates and the conditioned medium of Cos cells co-expressing pro-IGIF and ICE, but not in cells expressing either pro-IGIF or ICE alone (**Fig. 2B**).

These results indicate that ICE cleavage of pro-IGIF facilitates the export of mature, active IGIF from cells.

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Pro-IGIF is a Physiological Substrate of ICE In Vivo

To study the role of ICE in the proteolytic activation and export of IGIF under physiological conditions, we examined the processing of pro-IGIF and 5 export of mature IGIF from lipopolysaccharide (LPS)-activated Kupffer cells harvested from Propriobacterium acnes-elicited wild type and ICE deficient (ICE-/-) mice (**Example 25**).

As shown in **Fig. 3A**, Kupffer cells from 10 ICE-/- mice are defective in the export of IGIF. Kupffer cell lysates of wild type and ICE-/- mice contained similar amounts of IGIF as determined by ELISA. IGIF, however, could be detected only in the conditioned medium of wild type but not of the ICE-/- 15 cells. Thus, ICE-deficient (ICE-/-) mice synthesize pro-IGIF, but fail to export it as extracellular pro-or mature IGIF.

To determine whether ICE-deficient (ICE-/-) mice process intracellular pro-IGIF but fail to export 20 IGIF, Kupffer cells from wild type and ICE-/- mice were metabolically labeled with ³⁵S-methionine and IGIF immunoprecipitation experiments were performed on cell lysates and conditioned media as described in **Example 25**. These experiments demonstrated that unprocessed 25 pro-IGIF was present in both wild type and ICE-/- Kupffer cells. However, the 18-kDa mature IGIF was present only in the conditioned medium of wild type and not ICE-/- Kupffer cells (**Fig. 3B**). This shows that active ICE is required in cells for the export of 30 processed IGIF out of the cell.

In addition, conditioned medium from wild type but not from ICE-/- Kupffer cells contained IFN- γ inducing activity that was not attributed to the action

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of IL-12 because it was insensitive to a neutralizing anti-IL-12 antibody. The absence of IGIF in the conditioned medium of ICE-/- Kupffer cells is consistent with the finding in Cos cells that the processing of pro-IGIF by ICE is required for the export of active IGIF.

5 **Figs. 3C and 3D** show that, in vivo, ICE-/- mice have reduced serum levels of IGIF and IFN- γ , respectively. Wild type (ICE+/+) and ICE-/- mice (n=3) primed with heat-inactivated *P. acnes* were challenged with LPS (**Example 26**), and the levels of IGIF (**Fig. 3C**) and IFN- γ (**Fig. 3D**) in the sera of challenged mice were measured by ELISA three hours after LPS challenge (**Example 25**).

10 The sera of ICE-/- mice stimulated by *P. acnes* and LPS contained reduced levels of IGIF (**Fig. 3C**) and no detectable IFN- γ inducing activity in the presence of an anti-IL-12 antibody. The reduced serum levels of IGIF likely accounts for the 15 significantly lower levels of IFN- γ in the sera of ICE-/- mice (**Fig. 3D**), because we have observed no significant difference in the production of IL-12 in ICE-/- mice under these conditions. Consistent with this interpretation is the finding that non-adherent 20 splenocytes from wild type and ICE-/- mice produced similar amounts of IFN- γ when stimulated with recombinant active IGIF in vitro. Thus the impaired 25 production of IFN- γ is not due to any apparent defect in the T cells of the ICE-/- mice.

30 Taken together, these results establish a critical role for ICE in processing the IGIF precursor and in the export of active IGIF both in vitro and in

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vivo.

To examine in more detail the relationship between serum levels of IFN- γ and ICE activity in vivo, a time course after challenge of wild type and 5 ICE-deficient mice with LPS was performed (Example 26) (Fig. 4).

Fig. 4 shows a time course increase of serum IFN- γ in wild type mice, with sustained levels of ≥ 17 ng/ml occurring from 9-18 hrs after LPS challenge. 10 As predicted by the experiments discussed above, serum IFN- γ levels were significantly lower in ICE-/- mice, with a maximum of 2 ng/ml achieved over the same time period, which is approximately 15% of the level observed in wild type mice (Fig. 4).

15 Animals were also observed for clinical signs of sepsis and body temperature was measured at 4-hour intervals in wild type and ICE-/- mice challenged with 30 mg/kg or 100 mg/kg LPS (ICE-/-only). Results in Fig. 4 show that wild type mice experienced a 20 significant decrease in body temperature (from 36°C to 26°C) within 12 hours of LPS challenge. Signs of clinical sepsis were evident and all animals expired within 24-28 hours.

In contrast, ICE-/- mice challenged with 25 30 mg/kg LPS experienced only a 3°-4°C decrease in body temperature with minimal signs of distress and with no observed lethality. ICE-/- mice challenged with 100 mg/kg LPS experienced clinical symptoms, a decrease 30 in body temperature, and mortality similar to wild type mice at the 30 mg/kg LPS dose.

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The ICE Inhibitor Ac-YVAD-CHO is an Equipotent
Inhibitor of IL-1 β and IFN- γ Production

Since the processing and secretion of
5 biologically active IGIF is mediated by ICE, we
compared the activity of a reversible ICE inhibitor
(Ac-YVAD-CHO) on IL-1 β and IFN- γ production in a
peripheral blood mononuclear cell (PBMC) assay
(Examples 27).

10 Results in Fig. 5 show a similar potency for
the ability of the Ac-YVAD-CHO ICE inhibitor to
decrease IL-1 β and IFN- γ production in human PBMCs,
with an IC₅₀ of 2.5 μ M for each. Similar results were
obtained in studies with wild type mouse splenocytes.

15 These findings provide additional evidence
that pro-IGIF is a physiological substrate for ICE and
suggest that ICE inhibitors will be useful tools for
controlling physiological levels of IGIF and IFN- γ .

20 In summary, we have found that ICE controls
IGIF and IFN- γ levels in vivo and in vitro and that ICE
inhibitors can decrease levels of IGIF and IFN- γ in
human cells. These results have been described in co-
pending United States Application Serial No.
08/712,878, the disclosure of which is herein
25 incorporated by reference.

Compositions and Methods

The pharmaceutical compositions and methods
of this invention will be useful for controlling IL-1,
IGIF and IFN- γ levels in vivo. The methods and
30 compositions of this invention will thus be useful for
treating or reducing the advancement, severity of
effects of IL-1, IGIF- and IFN- γ -mediated conditions.

The compounds of this invention are effective ligands for ICE. Accordingly, these compounds are capable of targeting and inhibiting events in IL-1-, apoptosis-, IGIF-, and IFN- γ -mediated diseases, and, thus, the ultimate activity of that protein in inflammatory diseases, autoimmune diseases, destructive bone, proliferative disorders, infectious diseases, and degenerative diseases. For example, the compounds of this invention inhibit the conversion of precursor IL-1 β to mature IL-1 β by inhibiting ICE. Because ICE is essential for the production of mature IL-1, inhibition of that enzyme effectively blocks initiation of IL-1-mediated physiological effects and symptoms, such as inflammation, by inhibiting the production of mature IL-1. Thus, by inhibiting IL-1 β precursor activity, the compounds of this invention effectively function as IL-1 inhibitors.

Similarly, compounds of this invention inhibit the conversion of precursor IGIF to mature IGIF. Thus, by inhibiting IGIF production, the compounds of this invention effectively function as inhibitors of IFN- γ production.

Accordingly, one embodiment of this invention provides a method for decreasing IGIF production in a subject comprising the step of administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an ICE inhibitor and a pharmaceutically acceptable carrier.

Another embodiment of this invention provides a method for decreasing IFN- γ production in a subject comprising the step of administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an ICE inhibitor and a

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pharmaceutically acceptable carrier.

In another embodiment, the methods of this invention comprise the step of administering to a subject a pharmaceutical composition comprising an inhibitor of an ICE-related protease that is capable of cleaving pro-IGIF to active IGIF, and a pharmaceutically acceptable carrier. One such ICE-related protease is TX, as described above. This invention thus provides methods and pharmaceutical compositions for controlling IGIF and IFN- γ levels by administering a TX inhibitor.

Other ICE-related proteases capable of processing pro-IGIF into an active IGIF form may also be found. Thus it is envisioned that inhibitors of those enzymes may be identified by those of skill in the art and will also fall within the scope of this invention.

The compounds of this invention may be employed in a conventional manner for the treatment of diseases which are mediated by IL-1, apoptosis, IGIF or IFN- γ . Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a patient suffering from an IL-1-, apoptosis-, IGIF- or IFN- γ -mediated disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

Alternatively, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against IL-1-, apoptosis-, IGIF- or IFN- γ -mediated diseases over

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extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of ICE 5 inhibitors in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect 10 individuals over an extended period of time against IL-1-, apoptosis-, IGIF- or IFN- γ - mediated diseases.

The compounds of this invention may also be co-administered with other ICE inhibitors to increase the effect of therapy or prophylaxis against various 15 IL-1-, apoptosis, IGIF- or IFN- γ -mediated diseases.

In addition, the compounds of this invention may be used in combination either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxygenase inhibitors and antagonists of 20 cytokines other than IL-1 β .

The compounds of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, 25 interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO) or with prostaglandins, to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are 30 administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according

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to this invention comprise a combination of an ICE inhibitor of this invention and another therapeutic or prophylactic agent.

Pharmaceutical compositions of this invention
5 comprise any of the compounds of the present invention,
and pharmaceutically acceptable salts thereof, with any
pharmaceutically acceptable carrier, adjuvant or
vehicle. Pharmaceutically acceptable carriers,
adjuvants and vehicles that may be used in the
10 pharmaceutical compositions of this invention include,
but are not limited to, ion exchangers, alumina,
aluminum stearate, lecithin, self-emulsifying drug
delivery systems (SEDDS) such as d α -tocopherol
polyethyleneglycol 1000 succinate, or other similar
15 polymeric delivery matrices, serum proteins, such as
human serum albumin, buffer substances such as
phosphates, glycine, sorbic acid, potassium sorbate,
partial glyceride mixtures of saturated vegetable fatty
acids, water, salts or electrolytes, such as protamine
20 sulfate, disodium hydrogen phosphate, potassium
hydrogen phosphate, sodium chloride, zinc salts,
colloidal silica, magnesium trisilicate, polyvinyl
pyrrolidone, cellulose-based substances, polyethylene
glycol, sodium carboxymethylcellulose, polyacrylates,
25 waxes, polyethylene-polyoxypropylene-block polymers,
polyethylene glycol and wool fat. Cyclodextrins such
as α -, β - and γ -cyclodextrin, or chemically modified
derivatives such as hydroxyalkylcyclodextrins,
including 2-and 3-hydroxypropyl- β -cyclodextrines, or
30 other solubilized derivatives may also be
advantageously used to enhance delivery of compounds
of this invention.

The pharmaceutical compositions of this
invention may be administered orally, parenterally, by

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inhalation spray, topically, rectally, nasally,
buccally, vaginally or via an implanted reservoir. We
prefer oral administration. The pharmaceutical
compositions of this invention may contain any
5 conventional non-toxic pharmaceutically-acceptable
carriers, adjuvants or vehicles. In some cases, the pH
of the formulation may be adjusted with
pharmaceutically acceptable acids, bases or buffers to
enhance the stability of the formulated compounds or
10 its delivery form. The term parenteral as used herein
includes subcutaneous, intracutaneous, intravenous,
intramuscular, intra-articular, intrasynovial,
intrasternal, intrathecal, intralesional and
intracranial injection or infusion techniques.

15 The pharmaceutical compositions may be in the
form of a sterile injectable preparation, for example,
as a sterile injectable aqueous or oleaginous
suspension. This suspension may be formulated
according to techniques known in the art using suitable
20 dispersing or wetting agents (such as, for example,
Tween 80) and suspending agents. The sterile
injectable preparation may also be a sterile injectable
solution or suspension in a non-toxic parenterally-
acceptable diluent or solvent, for example, as a
25 solution in 1,3-butanediol. Among the acceptable
vehicles and solvents that may be employed are
mannitol, water, Ringer's solution and isotonic sodium
chloride solution. In addition, sterile, fixed oils
are conventionally employed as a solvent or suspending
30 medium. For this purpose, any bland fixed oil may be
employed including synthetic mono- or diglycerides.
Fatty acids, such as oleic acid and its glyceride
derivatives are useful in the preparation of
injectables, as are natural pharmaceutically-acceptable

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oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

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The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical

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composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-administered transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about 0.01 and about 30 100 mg/kg body weight per day, preferably between about 1 and 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of IL-1-, apoptosis, IGIF and IFN- γ -mediated

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diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, necrotic diseases, osteoarthritis, acute pancreatitis, 5 chronic pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs. host disease, osteoporosis, multiple myeloma-related bone 10 disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, 15 HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to 5 times per day or alternatively, as a continuous infusion. Such 20 administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated 25 and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a

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maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function 5 of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence or 10 disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of 15 factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, and the patient's disposition to the 20 disease and the judgment of the treating physician.

The IL-1 mediated diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, inflammatory diseases, autoimmune diseases, destructive bone disorders, 25 proliferative disorders, infectious diseases, and degenerative diseases. The apoptosis-mediated diseases which may be treated or prevented by the compounds of this invention include degenerative diseases.

Inflammatory diseases which may be treated or 30 prevented include, but are not limited to osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, and adult respiratory distress syndrome. Preferably the inflammatory disease is osteoarthritis or acute pancreatitis.

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Autoimmune diseases which may be treated or prevented include, but are not limited to, glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, 5 Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, 10 Crohn's disease, psoriasis, and graft vs. host disease. Preferably the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or psoriasis.

Destructive bone disorders which may be treated or prevented include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder. 15

Proliferative diseases which may be treated or prevented include, but are not limited to, acute 20 myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Infectious diseases which may be treated or prevented include, but are not limited to, sepsis, 25 septic shock, and Shigellosis.

The IL-1-mediated degenerative or necrotic diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, 30 cerebral ischemia, and myocardial ischemia. Preferably, the degenerative disease is Alzheimer's disease.

The apoptosis-mediated degenerative diseases which may be treated or prevented by the compounds of

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this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

The methods of this invention may be used for treating, or reducing the advancement, severity or effects of an IGIF- or IFN- γ -mediated inflammatory, autoimmune, infectious, proliferative, destructive bone, necrotic, and degenerative conditions, including diseases, disorders or effects, wherein the conditions are characterized by increased levels of IGIF or IFN- γ production.

Examples of such inflammatory conditions include, but are not limited to, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, cerebral ischemia, myocardial ischemia and adult respiratory distress syndrome.

Preferably, the inflammatory condition is rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis and adult respiratory distress syndrome.

Examples of such infectious conditions include, but are not limited to, infectious hepatitis, sepsis, septic shock and Shigellosis.

Examples of such autoimmune conditions include, but are not limited to, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune

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neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute 5 dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome.

Preferably the autoimmune condition is glomerulonephritis, insulin-dependent diabetes mellitus 10 (Type I), juvenile diabetes, psoriasis, graft vs. host disease, including transplant rejection, and hepatitis.

Examples of such destructive bone disorders include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

15 Examples of such proliferative conditions include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Examples of such neurodegenerative conditions 20 include, but are not limited to, Alzheimer's disease, Parkinson's disease and Huntington's disease.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating IL-1, apoptosis, IGIF- and IFN- γ -mediated 25 diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to ICE or other cysteine proteases. As commercial 30 reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide in biochemical or cellular assays for ICE and ICE homologs or may be derivatized to bind to a

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stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial cystine protease inhibitors will be evident to those of ordinary skill
5 in the art.

Process of Preparing N-Acylamino Compounds

The ICE inhibitors of this invention may be synthesized using conventional techniques.
Advantageously, these compounds are conveniently
10 synthesized from readily available starting materials.

The compounds of this invention are among the most readily synthesized ICE inhibitors known. Previously described ICE inhibitors often contain four or more chiral centers and numerous peptide linkages.
15 The relative ease with which the compounds of this invention can be synthesized represents an advantage in the large scale production of these compounds.

For example, compounds of this invention may be prepared using the processes described herein. As
20 can be appreciated by the skilled practitioner, these processes are not the only means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the
25 various synthetic steps described herein may be performed in an alternate sequence or order to give the desired compounds.

This invention also provides a preferred method for preparing the compounds of this invention.
30 Accordingly, in another embodiment (M) is provided a process for preparing an N-acylamino compound comprising the steps of:

- a) mixing a carboxylic acid with an N-

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alloc-protected amino in the presence of an inert solvent, triphenylphosphine, a nucleophilic scavenger, and tetrakis-triphenyl phosphine palladium(0) at ambient temperature under an inert atmosphere; and

5 b) adding to the step a) mixture, HOBT and EDC; and optionally comprising the further step of:

c) hydrolyzing the step b) mixture in the presence of a solution comprising an acid and H₂O, wherein the step b) mixture is optionally concentrated, 10 prior to hydrolyzing.

Preferably, the inert solvent is CH₂Cl₂, DMF, or a mixture of CH₂Cl₂ and DMF.

15 Preferably, the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine, or dimethyl barbituric acid. More preferably, the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

20 Preferably, the solution comprises trifluoroacetic acid in about 1-90% by weight. More preferably, the solution comprises trifluoroacetic acid in about 20-50% by weight.

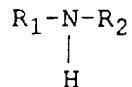
25 Alternatively, the solution comprises hydrochloric acid in about 0.1-30% by weight. More preferably, the solution comprises hydrochloric acid in about 0.1-30% by weight.

More preferably, in the above process, the inert solvent is CH₂Cl₂, DMF, or a mixture of CH₂Cl₂ and DMF and the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine, or dimethyl barbituric acid.

30 Most preferably, in the above process the inert solvent is CH₂Cl₂, DMF, or a mixture of CH₂Cl₂ and DMF and the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

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Preferably, the N-acyclamino compound is represented by formula (VIII):



5

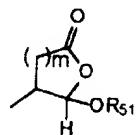
wherein:

R1 is as defined above in embodiment (A);

R2 is:

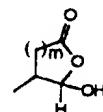
10

(a)



wherein R51 is as defined above in embodiment (B);

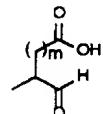
(b)



, or

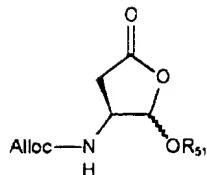
15

(c)



;

Preferably, the N-alloc-protected amine is:



, wherein R51 is as defined above.

20

In preferred processes, the substituents are as defined in embodiment (A).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R1 is as defined

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above in embodiment (B) and R₂ is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (B).
5

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R₁ is as defined above in embodiment (C) and R₂ is as defined above in embodiment (M).

10 Preferably in these alternative processes, the substituents are as defined above in embodiment (C).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R₁ is as defined above in embodiment (D) and R₂ is as defined above in embodiment (M).
15

Preferably in these alternative processes, the substituents are as defined above in embodiment (D).

20 Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R₁ is as defined above in embodiment (E) and R₂ is as defined above in embodiment (M).

25 Preferably in these alternative processes, the substituents are as defined above in embodiment (E).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R₁ is as defined above in embodiment (F) and R₂ is as defined above in embodiment (M).
30

Preferably in these alternative processes, the substituents are as defined above in embodiment (F).

Alternatively, the N-acylamino compound is

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represented by formula (VIII), wherein R₁ is as defined above in embodiment (G) and R₂ is as defined above in embodiment (G).

5 Preferably in these alternative processes, the substituents are as defined above in embodiment (G).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R₁ is as defined above in embodiment (H) and R₂ is as defined above in 10 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (H).

Alternatively, the N-acylamino compound is 15 represented by formula (VIII), wherein R₁ is as defined above in embodiment (I) and R₂ is as defined above in embodiment (M).

20 Preferably in these alternative processes, the substituents are as defined above in embodiment (I).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R₁ is as defined above in embodiment (J) and R₂ is as defined above in 25 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (J).

Alternatively, the N-acylamino compound is 30 represented by formula (VIII), wherein R₁ is as defined above in embodiment (K) and R₂ is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (K).

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Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R₁ is as defined above in embodiment (L) and R₂ is as defined above in embodiment (M).

5 Preferably in these alternative processes, the substituents are as defined above in embodiment (L).

In order that this invention be more fully understood, the following examples are set forth.

10 These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

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Example 1

Inhibition of ICE

We obtained inhibition constants (K_i) and IC_{50} values for compounds of this invention using the three methods described below:

1. Enzyme assay with UV-visible substrate

This assay is run using an Succinyl-Tyr-Val-Ala-Asp-pNitroanilide substrate. Synthesis of analogous substrates is described by L. A. Reiter (Int. 10 J. Peptide Protein Res. 43, 87-96 (1994)). The assay mixture contains:

65 μ l buffer (10mM Tris, 1 mM DTT, 0.1% CHAPS @pH 8.1)
10 μ l ICE (50 nM final concentration to give a rate of ~1mOD/min)

15 5 μ l DMSO/Inhibitor mixture
20 μ l 400 μ M Substrate (80 μ M final concentration)
100 μ l total reaction volume

The visible ICE assay is run in a 96-well microtiter plate. Buffer, ICE and DMSO (if inhibitor 20 is present) are added to the wells in the order listed. The components are left to incubate at room temperature for 15 minutes starting at the time that all components are present in all wells. The microtiter plate reader is set to incubate at 37 °C. After the 15 minute 25 incubation, substrate is added directly to the wells and the reaction is monitored by following the release of the chromophore (pNA) at 405 - 603 nm at 37 °C for 20 minutes. A linear fit of the data is performed and the rate is calculated in mOD/min. DMSO is only 30 present during experiments involving inhibitors, buffer is used to make up the volume to 100 μ l in the other experiments.

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2. Enzyme Assay with Fluorescent Substrate

This assay is run essentially according to Thornberry et al. (Nature 356: 768-774 (1992)), using substrate 17 referenced in that article. The substrate 5 is: Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC). The following components are mixed:

65 μ l buffer(10mM Tris, 1mM DTT, 0.1% CHAPS @pH8.1)
10 μ l ICE (2 - 10 nM final concentration)
5 μ l DMSO/inhibitor solution
10 20 μ l 150 μ M Substrate (30 μ M final)
100 μ l total reaction volume

The assay is run in a 96 well microtiter plate. Buffer and ICE are added to the wells. The components are left to incubate at 37 °C for 15 minutes 15 in a temperature-controlled wellplate. After the 15 minute incubation, the reaction is started by adding substrate directly to the wells and the reaction is monitored @37 °C for 30 minutes by following the release of the AMC fluorophore using an excitation 20 wavelength for 380 nm and an emission wavelength of 460 nm. A linear fit of the data for each well is performed and a rate is determined in fluorescence units per second.

For determination of enzyme inhibition 25 constants (K_i) or the mode of inhibition (competitive, uncompetitive or noncompetitive), the rate data determined in the enzyme assays at varying inhibitor concentrations are computer-fit to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, 30 Wiley-Interscience, 1975).

The determination of second order rate constants for irreversible inhibitors was performed by fitting the fluorescence vs time data to the progress equations of Morrison. Morrison, J.F., Mol. Cell.

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Biophys., 2, pp. 347-368 (1985). Thornberry et al. have published a description of these methods for measurement of rate constants of irreversible inhibitors of ICE. Thornberry, N.A., et al.

- 5 Biochemistry, 33, pp. 3923-3940 (1994). For compounds where no prior complex formation can be observed kinetically, the second order rate constants (k_{inact}) are derived directly from the slope of the linear plots of k_{obs} vs. [I]. For compounds where prior complex formation to the enzyme can be detected, the hyperbolic plots of k_{obs} vs. [I] are fit to the equation for saturation kinetics to first generate K_i and k' . The second order rate constant k_{inact} is then given by k'/K_i .

15 3. PBMC Cell assay

IL-1 β Assay with a Mixed Population of Human Peripheral Blood Mononuclear Cells (PBMC) or Enriched Adherent Mononuclear Cells

- Processing of pre-IL-1 β by ICE can be measured in cell culture using a variety of cell sources. Human PBMC obtained from healthy donors provides a mixed population of lymphocyte subtypes and mononuclear cells that produce a spectrum of interleukins and cytokines in response to many classes of physiological stimulators. Adherent mononuclear cells from PBMC provides an enriched source of normal monocytes for selective studies of cytokine production by activated cells.

Experimental Procedure:

- An initial dilution series of test compound in DMSO or ethanol is prepared, with a subsequent dilution into RPMI-10% FBS media (containing 2 mM L-glutamine, 10 mM HEPES, 50 U and 50 ug/ml pen/strep)

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respectively to yield drugs at 4x the final test concentration containing 0.4% DMSO or 0.4% ethanol. The final concentration of DMSO is 0.1% for all drug dilutions. A concentration titration which brackets 5 the apparent K_i for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen.

Generally 5-6 compound dilutions are tested and the cellular component of the assay is performed in 10 duplicate, with duplicate ELISA determinations on each cell culture supernatant.

PBMC Isolation and IL-1 Assay:

Buffy coat cells isolated from one pint human blood (yielding 40-45 ml final volume plasma plus 15 cells) are diluted with media to 80 ml and LeukoPREP separation tubes (Becton Dickinson) are each overlaid with 10 ml of cell suspension. After 15 min centrifugation at 1500-1800 xg, the plasma/media layer is aspirated and then the mononuclear cell layer is 20 collected with a Pasteur pipette and transferred to a 15 ml conical centrifuge tube (Corning). Media is added to bring the volume to 15 ml, gently mix the cells by inversion and centrifuge at 300 xg for 15 min. Resuspend the PBMC pellet in a small volume of media, 25 count cells and adjust to 6×10^6 cells/ml.

For the cellular assay, 1.0 ml of the cell suspension is added to each well of a 24-well flat bottom tissue culture plate (Corning), 0.5 ml test compound dilution and 0.5 ml LPS solution (Sigma 30 #L-3012; 20 ng/ml solution prepared in complete RPMI media; final LPS concentration 5 ng/ml). The 0.5 ml additions of test compound and LPS are usually sufficient to mix the contents of the wells. Three control mixtures are run per experiment, with either

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LPS alone, solvent vehicle control, and/or additional media to adjust the final culture volume to 2.0 ml. The cell cultures are incubated for 16-18 hr at 37 °C in the presence of 5% CO₂.

5 At the end of the incubation period, cells are harvested and transferred to 15 ml conical centrifuge tubes. After centrifugation for 10 min at 200 xg, supernatants are harvested and transferred to 1.5 ml Eppendorf tubes. It may be noted that the cell 10 pellet may be utilized for a biochemical evaluation of pre-IL-1β and/or mature IL-1β content in cytosol extracts by western blotting or ELISA with pre-IL-1β specific antisera.

Isolation of Adherent Mononuclear cells:

15 PBMC are isolated and prepared as described above. Media (1.0 ml) is first added to wells followed by 0.5 ml of the PBMC suspension. After a one hour incubation, plates are gently shaken and nonadherent cells aspirated from each well. Wells are then gently 20 washed three times with 1.0 ml of media and final resuspended in 1.0 ml media. The enrichment for adherent cells generally yields 2.5-3.0 × 10⁵ cells per well. The addition of test compounds, LPS, cell 25 incubation conditions and processing of supernatants proceeds as described above.

ELISA:

We have used Quantikine kits (R&D Systems) for measurement of mature IL-1β. Assays are performed according to the manufacturer's directions. Mature 30 IL-1β levels of about 1-3 ng/ml in both PBMC and adherent mononuclear cell positive controls are observed. ELISA assays are performed on 1:5, 1:10 and 1:20 dilutions of supernatants from LPS-positive

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controls to select the optimal dilution for supernatants in the test panel.

The inhibitory potency of the compounds can be represented by an IC₅₀ value, which is the 5 concentration of inhibitor at which 50% of mature IL-1 β is detected in the supernatant as compared to the positive controls.

The skilled practitioner realizes that values obtained in cell assays, such as those described 10 herein, can depend on multiple factors, such as cell type, cell source, growth conditions and the like.

Example 2

Pharmacokinetic Studies in the Mouse

15 Peptidyl ICE inhibitors are cleared rapidly with clearance rates greater than 100 μ /min/kg. Compounds with lower clearance rates have improved pharmacokinetic properties relative to peptidyl ICE inhibitors.

20 We obtained the rate of clearance in the mouse (μ /min/kg) for several compounds of this invention using the method described below:

Sample Preparation and Dosing

Compounds were dissolved in sterile TRIS 25 solution (0.02M or 0.05M) at a concentration of 2.5mg/ml. Where necessary to ensure a complete solution, the sample was first dissolved in a minimum of dimethylacetamide (maximum of 5% of total solution volume) then diluted with the TRIS solution.

30 The drug solution was administered to CD-1 mice (Charles River Laboratories - 26-31g) via the tail

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vein at a dose volume of 10ml/kg giving a drug dose of 25mg/kg.

Mice were dosed in groups of 5 for each timepoint (generally from 2 minutes to 2 hours) then at 5 the appropriate time the animals were anaesthetised with halothane and the blood collected into individual heparinized tubes by jugular severance. The blood samples were cooled to 0 °C then the plasma separated and stored at -20 °C until assayed.

10 Bioassay

Drug concentration in the plasma samples were determined by HPLC analysis with UV or MS (ESP) detection. Reverse phase chromatography was employed using a variety of bonded phases from C1 to C18 with 15 eluents composed of aqueous buffer/acetonitrile mixtures run under isocratic conditions.

Quantitation was by external standard methods with calibration curves constructed by spiking plasma with drug solutions to give concentrations in the range 20 of 0.5 to 50µg/ml.

Prior to analysis the plasma samples were deproteinated by the addition of acetonitrile, methanol, trichloroacetic acid or perchloric acid followed by centrifugation at 10,000g for 10 minutes. 25 Sample volumes of 20µl to 50µl were injected for analysis.

Compound 214e

Dosing and sampling

The drug was dissolved in sterile 0.02M Tris 30 to give a 2.5mg/ml solution which was administered to 11 groups of 5 male CD-1 mice via the tail vein at a dose of 25mg/kg. At each of the following timepoints: 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes a

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group of animals was anaesthetised and the blood collected into heparinized tubes. After separation the plasma was stored at -20 °C until assayed.

Assay

5 Aliquots of plasma (150µl) were treated with 5% perchloric acid (5µl) then mixed by vortexing and allowed to stand for 90 minutes prior to centrifugation. The resulting supernatant was separated and 20µl was injected for HPLC analysis.

10 HPLC Conditions

Column	100 x 4.6mm	Kromasil KR 100 5C4
Mobile Phase	0.1m Tris pH7.5	86%
	Acetonitrile	14%
Flowrate	1ml/min	
15 Detection	UV at 210nm	
	Retention Time 3.4 mins	

The results of the analysis indicated a decrease in the mean plasma level of the drug from ~ 70µg/ml at 2 minutes to < 2µg/ml at 90 and 120 minutes.

20 Compound 217e

Dosing and sampling

The drug was dissolved in sterile 0.02M Tris to give a 2.5mg/ml solution which was administered to 11 groups of 5 male CD-1 mice via the tail vein at a dose of 25mg/kg. At each of the following timepoints: 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes a group of animals was anaesthetised and the blood collected into heparinized tubes. After separation the plasma was stored at -20 °C until assayed.

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Assay

Aliquots of plasma (100 μ l) were diluted with acetonitrile (100 μ l) then mixed by vortexing for 20 seconds before centrifugation for 10 minutes. The 5 resulting supernatant was separated and 20 μ l was injected for HPLC analysis.

HPLC Conditions

Column	150 x 4.6mm	Zorbax SBC8
Mobile Phase	0.05M Phosphate buffer pH7.1	72%
	Acetonitrile	28%
Flowrate	1.4ml/min	
Detection	UV at 210nm	
Retention Time	3.0 and 3.6 mins (diasteromers)	

15 The results of the analysis indicated a decrease in mean plasma concentrations from ~ 55 μ g/ml at 2 minutes to < 0.2 μ g/ml at 60-120 minutes.

Example 3

Peptidyl ICE inhibitors are cleared rapidly 20 with clearance rates greater than 80 ml/min/kg. Compounds with lower clearance rates have improved pharmacokinetic properties relative to peptidyl ICE inhibitors.

We obtained the rate of clearance in the rat 25 (ml/min/kg) for several compounds of this invention using the method described below:

In vivo Rat Clearance Assay

Cannulations of the jugular and carotid vessels of rats under anesthesia were performed one day 30 prior to the pharmacokinetic study. M.J. Free, R.A.

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Jaffee; 'Cannulation techniques for the collection blood and other bodily fluids'; in: Animal Models; p. 480-495; N.J. Alexander, Ed.; Academic Press; (1978). Drug (10mg/mL) was administered via the 5 jugular vein in a vehicle usually consisting of: propylene glycol/saline, containing 100mM sodium bicarbonate in a 1:1 ratio. Animals were dosed with 10-20 mg drug/kg and blood samples were drawn at 0, 2, 5, 7, 10, 15, 20, 30, 60, and 90 minutes from an 10 indwelling carotid catheter. The blood was centrifuged to plasma and stored at -20 °C until analysis. Pharmacokinetic analysis of data was performed by non-linear regression using standard software such as RStrip (MicroMath Software, UT) and/or Pcononlin (SCI 15 Software, NC) to obtain clearance values.

Analytical:

Rat plasma was extracted with an equal volume of acetonitrile (containing 0.1% TFA). Samples were then centrifuged at approximately 1,000 x g and the 20 supernatant analyzed by gradient HPLC. A typical assay procedure is described below.

200 µL of plasma was precipitated with 200 µL of 0.1% trifluoroacetic acid (TFA) in acetonitrile and 10 µL of a 50% aqueous zinc chloride solution, vortexed 25 then centrifuged at ~1000 x g and the supernatant collected and analyzed by HPLC.

HPLC procedure:

Column: Zorbax SB-CN (4.6 x 150 mm) (5µ particle size)
30 Column temperature: 50 °C
Flow rate: 1.0 mL/min
Injection volume: 75 µL.
Mobile phase: A=0.1% TFA in water and B=100% acetonitrile

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Gradient employed: 100% A to 30% A in 15.5 min
0% A at 16 min
100% A at 19.2 min
Wavelength: 214 nm

5 A standard curve was run at 20, 10, 5, 2 and
1 µg/mL concentrations.

Example 4

Whole Blood Assay for IL-1 β Production

We obtained IC₅₀ values for several compounds
10 of this invention using the method described below:

Purpose:

The whole blood assay is a simple method for
measuring the production of IL-1 β (or other cytokines)
and the activity of potential inhibitors. The
15 complexity of this assay system, with its full
complement of lymphoid and inflammatory cell types,
spectrum of plasma proteins and red blood cells is an
ideal in vitro representation of human in vivo
physiologic conditions.

20 Materials:

Pyrogen-free syringes (~ 30 cc)

Pyrogen-free sterile vacuum tubes containing
lyophilized Na₂EDTA (4.5 mg/10 ml tube)

Human whole blood sample (~ 30-50 cc)

25 1.5 ml eppendorf tubes

Test compound stock solutions (~ 25mM in DMSO or other
solvent)

Endotoxin-free sodium chloride solution (0.9%) and HBSS
Lipopolysaccharide (Sigma; Cat.# L-3012) stock solution

30 at 1mg/ml in HBSS

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IL-1 β ELISA Kit (R & D Systems; Cat # DLB50)

TNF α ELISA Kit (R & D Systems; Cat # DTA50)

Water bath or incubator

Whole Blood Assay Experimental Procedure:

- 5 Set incubator or water bath at 30 °C.
Aliquot 0.25ml of blood into 1.5 ml eppendorf tubes.
Note: be sure to invert the whole blood sample tubes
after every two aliquots. Differences in replicates
may result if the cells sediment and are not uniformly
10 suspended. Use of a positive displacement pipette will
also minimize differences between replicate aliquots.

- Prepare drug dilutions in sterile pyrogen-free saline by serial dilution. A dilution series which brackets the apparent K_i for a test compound
15 determined in an ICE inhibition assay is generally used for the primary compound screen. For extremely hydrophobic compounds, we have prepared compound dilutions in fresh plasma obtained from the same blood donor or in PBS-containing 5% DMSO to enhance
20 solubility.

- Add 25 μ l test compound dilution or vehicle control and gently mix the sample. Then add 5.0 μ l LPS solution (250 ng/ml stocked prepared fresh: 5.0 ng/ml final concentration LPS), and mix again. Incubate the
25 tubes at 30 °C in a water bath for 16-18 hr with occasional mixing. Alternatively, the tubes can be placed in a rotator set at 4 rpm for the same incubation period. This assay should be set up in duplicate or triplicate with the following controls:
30 negative control- no LPS; positive control- no test inhibitor; vehicle control- the highest concentration of DMSO or compound solvent used in the experiment.

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Additional saline is added to all control tubes to normalize volumes for both control and experimental whole blood test samples

After the incubation period, whole blood 5 samples are centrifuged for 10 minutes at ~ 2000 rpm in the microfuge, plasma is transferred to a fresh microfuge tube and centrifuged at 1000 x g to pellet residual platelets if necessary. Plasma samples may be stored frozen at -70 °C prior to assay for cytokine 10 levels by ELISA.

ELISA:

We have used R & D Systems (614 McKinley Place N.E. Minneapolis, MN 55413) Quantikine kits for measurement of IL-1 β and TNF- α . The assays are 15 performed according to the manufacturer's directions. We have observed IL-1 β levels of ~ 1-5 ng/ml in positive controls among a range of individuals. A 1:200 dilution of plasma for all samples has been sufficient in our experiments for ELISA results to fall 20 on the linear range of the ELISA standard curves. It may be necessary to optimize standard dilutions if you observe differences in the whole blood assay. Nerad, J.L. et al., J. Leukocyte Biol., 52, pp. 687-692 (1992).

25

Example 5

Inhibition of ICE homologs

1. Isolation of ICE homologs

Expression of TX in insect cells using a baculovirus expression system. We have subcloned Tx cDNA (Faucheu 30 et al., supra 1995) into a modified pVL1393 transfer

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vector, co-transfected the resultant plasmid (pVL1393/TX) into insect cells with viral DNA and identified the recombinant baculovirus. After the generation of high titer recombinant virus stock, the 5 medium was examined for TX activity using the visible ICE assay. Typically, infection of Spodoptera frugiperda (Sf9) insect cells at an MOI of 5 with recombinant virus stock resulted in a maximum expression after 48 hours of 4.7 μ g/ml. ICE was used as 10 a standard in the assay.

Amino terminal T7 tagged versions of ICE or TX were also expressed. Designed originally to assist the identification and purification of the recombinant proteins, the various constructs have also allowed 15 examination of different levels of expression and of the relative levels of apoptosis experienced by the different homologs. Apoptosis in the infected Sf9 cells (examined using a Trypan Blue exclusion assay) was increased in the lines expressing ICE or TX 20 relative to cells infected with the viral DNA alone.

Expression and purification of N-terminally (His)₆-tagged CPP32 in *E. coli*. A cDNA encoding a CPP32 (Fernandes-Alnemri et al, supra 1994) polypeptide starting at Ser (29) was PCR amplified with primers 25 that add in frame XhoI sites to both the 5' and 3' ends of the cDNA and the resulting XhoI fragment ligated into a Xho I-cut pET-15b expression vector to create an in frame fusion with (his)₆ tag at the n-terminus of the fusion protein. The predicted recombinant protein 30 starts with the amino acid sequence of MGSSHHHHHHSSGLVPRGSHMLE, where LVPRGS represents a thrombin cleavage site, followed by CPP32 starting at

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Ser (29). *E. coli* BL21(DE3) carrying the plasmid were grown to log phase at 30 °C and were then induced with 0.8 mM IPTG. Cells were harvested two hours after IPTG addition. Lysates were prepared and soluble proteins 5 were purified by Ni-agarose chromatography. All of the expressed CPP32 protein was in the processed form. N-terminal sequencing analysis indicated that the processing occurred at the authentic site between Asp (175) and Ser (176). Approximately 50 µg of CPP32 10 protein from 200 ml culture. As determined by active site titration, the purified proteins were fully active. The protease preparation were also very active in vitro in cleaving PARP as well as the synthetic DEVD-AMC substrate (Nicholson et al, supra 1995).

15 2. Inhibition of ICE homologs

The selectivity of a panel of reversible inhibitors for ICE homologs is depicted in Table 1. ICE enzyme assays were performed according to Wilson et al (supra 1994) using a YVAD-AMC substrate (Thornberry et al, supra 1992). Assay of TX activity was performed using the ICE substrate under identical conditions to ICE. Assay 20 of CPP32 was performed using a DEVD-AMC substrate (Nicholson et al., supra 1995). In general, there is low selectivity between ICE and TX for a wide range of 25 scaffolds. None of the synthetic ICE compounds tested are effective inhibitors of CPP32. Assay of the reversible compounds at the highest concentration (1 µM) revealed no inhibition.

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Table 1

Compound	K _i ICE (nM)	K _i TX (nM)	K _i CPP32 (nM)
214e	7.5	7.0 ± 1.1	> 1000
135a	90	55 ± 9	>1000
5 125b	60	57 ± 13	> 1000
137	40	40 ± 7	> 1000

Second-order rate constants for inactivation of ICE and ICE homologs with selected irreversible inhibitors are presented below (Table 2). The 10 irreversible compounds studied are broad spectrum inhibitors of ICE and its homologs. Some selectivity, however, is observed with the irreversible compounds comparing inhibition of ICE and CPP32.

Table 2

15	Compound	k _{inact}	k _{inact} (TX)	k _{inact}
		(ICE)		(CPP32)
		M ⁻¹ s ⁻¹	M ⁻¹ s ⁻¹	M ⁻¹ s ⁻¹
	138	120,000	150,000	550,000
	217d	475,000	250,000	150,000
	108a	100,000	25,000	nd

Example 6

20 Inhibition of apoptosis

Fas-Induced Apoptosis in U937 cells. Compounds were evaluated for their ability to block anti-Fas-induced apoptosis. In a preliminary experiment using RT-PCR, 25 we detected mRNA encoding ICE, TX, ICH-1, CPP32 and

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CMH-1 in unstimulated U937 cells. We used this cell line for apoptosis studies. U937 cells were seeded in culture at 1×10^5 cells/ml and grown to $\sim 5 \times 10^6$ cells/ml. For apoptosis experiments, 2×10^6 cells 5 were plated in 24-well tissue culture plates in 1 ml RPMI-1640-10% FBS and stimulated with 100 ng/ml anti-Fas antigen antibody (Medical and Biological Laboratories, Ltd.). After a 24 hr incubation at 37 °C, the percentage of apoptotic cells was determined by 10 FACS analysis using ApoTag reagents.

All compounds were tested initially at 20 μM and titrations were performed with active compounds to determine IC₅₀ values. Inhibition of apoptosis (> 75% at 20 μM) was observed for 108a, 136, and 138. 15 An IC₅₀ of 0.8 μM was determined for 217e compared to no inhibition of anti-Fas-induced apoptosis by 214e at 20 μM .

Example 7

20 In vivo acute assay for efficacy as
 anti-inflammatory agent

LPS-Induced IL-1 β Production.

Efficacy of 214e and 217e was evaluated in CD1 mice (n=6 per condition) challenged with LPS (20 mg/kg IP). The test compounds were prepared in olive 25 oil:DMSO:ethanol (90:5:5) and administered by IP injection one hour after LPS. Blood was collected seven hours after LPS challenge. Serum IL-1 β levels were measure by ELISA. Results in Fig. 6 show a dose dependent inhibition of IL-1 β secretion by 214e, with

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an ED₅₀ of approximately 15 mg/kg. Similar results were obtained in a second experiment. A significant inhibition of IL-1 β secretion was also observed in 217e treated mice (Fig. 7). However, a clear dose response 5 was not apparent.

Compounds 214e and 217e (50 mg/kg) were also administered by oral gavage to assess absorption. Results in Fig. 8 show that 214e, but not 217e when administered orally inhibited IL-1 β secretion, 10 suggesting potential for oral efficacy of ICE inhibitors as anti-inflammatory agents.

The efficacy of analogs of 214e were also evaluated in LPS challenged mice after IP administration (Fig. 9) and PO administration 15 (Fig. 10).

Table 3 % Inhibition of IL- β production by analogs of 214e in LPS-challenged mice after PO and IP administration (50 mg/kg).

Table 3

Compound	PO% Inhibition	IP% Inhibition
214e	75	78
265	27	30
416	52	39
434	80	74
438	13	40
442	10	0
2002	-	78

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Table 4

Comparison of 214e Prodrugs for
Efficacy in LPS Challenged Mice:
Time Course Inhibition of IL-1 β Production

Time of Compound Administration (relative to time of LPS challenge, PO, 50 mg/kg)				
	Compound	-2 hr	-1 hr	0 hr
5	214e	39*	-*	80*
		43*	44*	48*
		-*	-*	-*
	304a	30	33	68
	2100e	49	54	94
	2100a	8	71	67
	213e	0	48	41
	302	0	27	21
	2100c	0	0	85
10	2100d	42	35	52
	2100b	0	0	47
	2001	~63 64*	~62 62*	~57 58*
				~54 55*
15				

* Values obtained in subsequent assays

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Example 8

Measurement of blood levels of prodrugs of 214e.

Mice were administered a p.o. dose of compounds **302** and **304a** (50 mg/kg) prepared in 0.5 % carboxymethylcellulose. Blood samples were collected at 1 and 7 hours after dosing. Serum was extracted by precipitation with an equal volume of acetonitrile containing 2 % formic acid followed by centrifugation. The supernatant was analyzed by liquid chromatography-mass spectrometry (ESI-MS) with a detection level of 0.03 to 3 µg/ml. Compounds **302** and **304a** showed detectable blood levels when administered orally, **214e** itself shows no blood levels above 0.10 µg/mL when administered orally. Compounds **302** and **304a** are prodrugs of **214e** and are metabolized to **214e** in vivo (see Fig. 11).

Example 9

We obtained the following data (see Tables 5 and 6) for compounds of this invention using the methods described in Examples 1-8. The structures of the compounds of Example 9 are shown in Example 10-17.

Table 5

Compound	UV- Visible Ki (nM)	Cell	Whole	Clearance	Clearance
		PBMC avg.	human blood	Mouse, i.v.	Rat, i.v. ml/min/kg
		IC50 (nM)	IC50 (nM)		ml/min/kg
47b	27	1800	<600	338	
47a	19	2600	5100	79	32
135a	90	2800	5000	>100	

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	Compound	UV- Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	135b	320	1600	1700		
	125b	60	800	4500		
5	108b	400	25000			>100
	137	40	1700	14000		
	139	350	2000			
	213e	130	900	600 400*		
	214c	1200	5000			
	214e	7.5	1600	1300	23	12
10	217c		1700	7000	70	
	217e		175	2000	>50	
	220b	600	2125			
	223b	99	5000		>100	
15	223e	1.6	3000	>20000	89	
	226e	15	1100	1800	109	
	227e	7	234	550		
	230e		325	300	67	
	232e	1100	4500		22	26
	235e	510	4750		36	
	238e	500	4250			
20	246	12	950	10000	31	
	257	13	11000 6600*			
	265	47	4300	1400	23	20
	281	50	600 2500*			
25	302	4500	>20000	>20000		
	304a	200	1,400 14000*	2400 14000*		
	307a	55	14500	16000		
	307b	165		14000		
	404	2.9	1650 1800*	1100	64	24
	405	6.5	1700	2100		
30	406	4	1650	2300		
	407	0.4	540	1700		
	408	0.5	1100	1000	41	23

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Compound	UV- Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
409	3.7	2500			
410	17	2000	2800	32	20
411	0.9	540	1900		
412	1.3	580 660*	700 1000*		25
5	413	750	6200		
	415	2.5	990 1000*	450 3500*	26 18
	416	12	1200	3400	47
	417	8	2000	6000	33 22
	418	2.2	1050 2200*	7800 1800*	13 5.9
10	419	280	>8000		
	420	1200	8000 >8000*		
	421	200	4300 4600*		
	422	50	2200	1200	
	423	10	2100 1800*	1500	45
15	424	45	2500	4000	
	425	0.8	650 700*	650	
	426	90	4500 2500*		
	427	180	4500		36
	428	280			
20	429	7000			
	430	60	>8000		
	431	8	>8000	8000	
	432	1.6	560	2000	
	433	2.9	1000 1100*	1100	
25	434	4.9	1600 1200*	1800 1300*	20
	435	8	4400		
	436	7.5	2700		
	437	12	1800	5000	

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Compound	UV- Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
5	438	28	1000 700 2900*		22
	439	3.7	2800 3200 3400*		
	440	2.3	5000 2000		
	441	1	2500 4500		
	442	3.2	900 2000		54
	443	3.6	2800 1500		
	444	15	3500 3500		
	445	135	4000		
	446	62	3000		
	447	5.8	2500 1500		
10	448	130	4000		
	449	12	1500 3200 13000*		
	450	5	800 2200 1700*	18	12
	451	4	1800 1500 9000*		
	452	4.5	600 800* 650 1600*		27.3
	453	0.65	1300 1900 1600*		
	454	45	2500		
	455	1.2	400 2800 2600*		54
	456	4.5	600 1300* 600 1400*		12.7
	457	6.2	2000 3500		
15	458	20	2900		
	459	5	1800		
	460	115	400 2400		
	461	47			
	462	40			
	463	14	2400 2800*		
	464	2.5	1000 >1000 2500*		
	465	3	1000 800		

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Compound	UV- Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
466	0.8	1400	600		
467	11	1900			
468	4.5	850	2500		
470	5	500	360 500*		63
5	471	1	750	400	17
	472	140			
	473	1	1000	400 450*	
	474	85			
	475	5.5	690 650*	400 350*	31 21
10	476	7	1600	2500	
	477	60			
	478	380			
	479	15	900	700 2400*	
	480	25	2300		
15	481	1.2	390 930*	600 500*	34
	482	<0.2	340	380 260*	
	483	1.7	900	700	
	484	2	1550 1400*	5000	15
	485	2	900	900	
20	486	2.3	480 570*	500	37
	487	2.4	650 950*	500 400*	20
	488	1.5	940	750	
	489	6	2250 1700*	15000	
	490	4.3	980 1000*	700 1900*	
25	491	5	2500		
	493	25	1200	800 850*	

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	Compound	UV- Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	494	15	1350 1500*	7000		
5	495	43				
	496	16	1550 1600*	6000		
	497	3.5	740	350 700*		
	498	1.5	560	500 400*		
	499	3.5	1200 800*	9000		
10	605a	90	2600	>20000		
	605b	45	10000		97	
	605c	615	4500		37	
	605d	95	5100	16000 5100*	33	
	605e	29	2250	>10000		24
	605f	475	12500			
15	605g	165	22500			
	605h	460	>25000			
	605i	680	>20000			
	605j	110	8750		71	
	605m	650	20000			
20	605n	12	2100	>20000	28	
	605o	72		18000		
	605p	125	3200	>20000		
	605q	1000				
	605s	150	6000			
	605t	33				
25	609a	114	>30000			
	609b	27	>20000			
	619	300				
	620	35	1000	19000		
	621	7.2	1300	>20000		
30	622	35	1300	>20000		
	623	9				
	624	300				

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Compound	UV- Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
625	105				
626	260				
627	43	3250	8000		
628	36	2750	>20000		
5	629	230			
630	270				
631	805				
632	148				
10	633	92	5750	20000	
634	1400				
635	55	1900 3400*	4000		
605v	1100	>30000			
2201	9	2000 3700*	3500		60
15	2100e	250	800	600	
2100a	100	1100	850		
2002	4	810 860*	70 1400*		32
2100d	>100000	>20000	>20000		
2100c	7400	>20000	>20000		
20	2100b	8000	>20000	>20000	
2001	135	1800	3500		
1027	4000	>20000	>20000		60
25	1015	40	2500	1700	23

Table 6

Compound	Fluorescent Assay k _{inact} M ⁻¹ s ⁻¹	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
25	108a	1x10 ⁵	17500		
	136	5.4x10 ⁵	870	2800	93

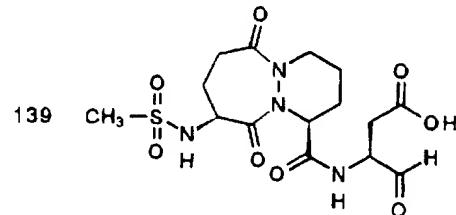
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Compound	Fluorescent Assay k_{inact} $M^{-1} s^{-1}$	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
138	1.2×10^5	900	2900	116	
217d	4.7×10^5	340	4000		
280	4×10^5	650	>1000		187
283	1×10^5	<200	450		104
284	3.5×10^5	470	550	77	100
285	4.3×10^5	810	1000	130	50

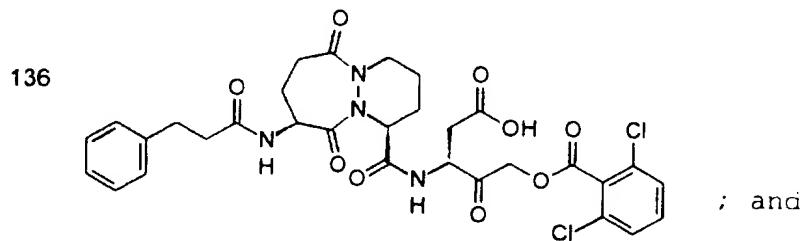
* Values obtained upon reassay.

Example 10

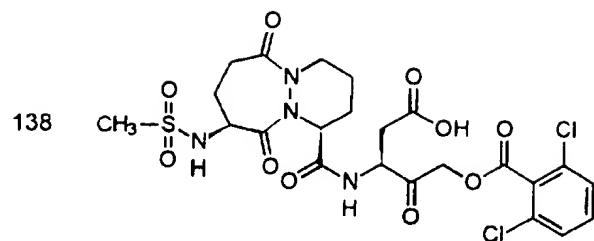
Compound 139 was synthesized by a method similar to the method used to synthesize 47a.



Compounds 136 and 138 were synthesized by a method similar to the method used to synthesize 57b.

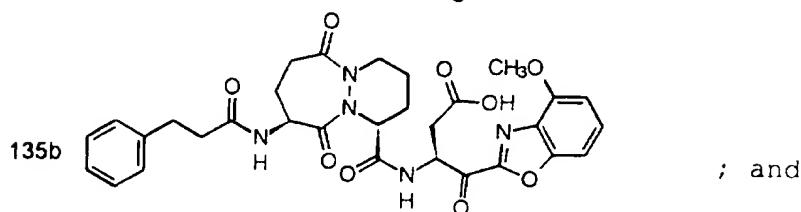
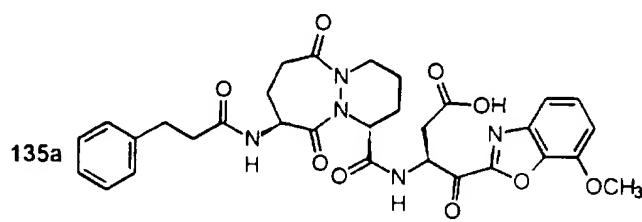


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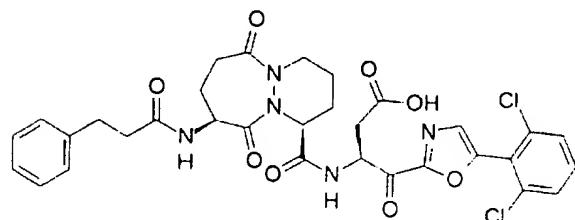


Compounds 135a, 135b, and 137 were synthesized by a method similar to the method used to synthesize 69a.

5



137



Compounds 813e, 814c, 814e, 817c, 817d, 817e,
820b, 823b, 823e, 826e, 827e, 830e, 832e, 835e, 838e,
13 846, 857, 865, 902, 904a, 907a, 907b, 1004-1013, 1015-

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1045, 1046-1068, 1070-1091, and 1093-1099 were synthesized by methods similar to those used to synthesize compound 264 and the corresponding compounds in Examples 10 and 11.

5 Compounds 47a, 47b, 108a, 108b, 125b, 213e, 214c, 217c, 217d, 217e, 220b, 223b, 223e, 226e, 227e, 230e, 232e, 235e, 238e, 246, 257, 264, 265, 280-287, 302, 304a, 307a, and 307b were synthesized as described below.

10 H. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-oxobutanoic acid.

Step A. N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

Reaction of N-tert-butoxycarbonylpipeolic acid (460 mg, 2.0 mmol) and N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (530 mg, 1.82 mmol) was carried out by a method analogous to that reported by Chapman (Bioorg. & Med. Chem. Lett. 2, pp. 613-618, (1992)) to give 654 mg of the title compound.

20 ^1H NMR (500 MHz, CDCl_3 (existing as rotamers)) δ 7.35 (m, 5H), 6.88 (br. s, 1H), 4.9-4.45 (m, 4H), 3.95+ (br. m, 2H), 3.06 (m, 1H), 2.9 (m, 1H), 2.7 (br. m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 1.7-1.5 (m, 3H), 1.45 (two s, 9H).

25 Step B. N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxo-tetrahydrofuran (654 mg) was dissolved in 15 ml of 25% trifluoroacetic acid in dichloromethane

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and stirred at room temperature. The mixture was concentrated to give a gummy residue. The residue was dissolved in dichloromethane and washed with 10% sodium bicarbonate. The organic layer was dried over 5 anhydrous sodium sulfate, filtered, and concentrated to give 422 mg of the title compound as a beige solid.

¹H NMR (500 MHz, CDCl₃) δ 7.38 (m, 5H), 7.15 (d, 1H), 5.55 (d, 1H), 4.95-4.8 (m, 1H), 4.78 (m, 1H), 10 4.65 (d, 1H), 4.45 (m, 1H), 3.2 (m, 0.5H), 3.05 (m, 0.5H), 2.95 (m, 0.5H), 2.85 (m, 0.5H), 2.65 (m, 1H), 2.55-2.38 (m, 1H), 1.95 (m, 1H), 1.8 (m, 1H), 1.6 (m, 2H), 1.38 (m, 2H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

N-Acetyl-tyrosinyl-valine (464 mg, 1.44 mmol) and N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (412 mg, 1.3 mmol) were dissolved in 5 ml each of dimethylformamide and dichloromethane and 20 cooled to 0°C. To the cooled solution was added 1-hydroxybenzotriazole (HOBT; 210 mg, 1.56 mmol) followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC; 326 mg, 1.7 mmol). After stirring for 18 hours, the mixture was 25 diluted with ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was concentrated to give a crude solid that was purified by flash chromatography (SiO₂) eluting with 94:6:1

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(dichloromethane:isopropanol:pyridine) to give 370 mg of the title compound.

10 ¹H NMR (500 MHz, CD₃OD (existing as diastereomers as well as rotamers)) δ 7.35 (m, 5H), 7.05 (m, 2H), 6.68 (m, 2H), 5.65 & 5.25 (m, 1H), 4.9-3.95 (m, 8H), 3.4-2.6 (m, 4H), 2.5-2.1 (m, 1H), 1.98 (s, 1H), 1.9 (s, 1H), 1.85 (s, 1H), 1.8-1.6 (m, 2H), 1.55-1.3 (m, 4H), 0.95-0.85 (m, 6H).

Step D. N-(N-Acetyl-tyrosinyl-valinyl-pipocolyl)-3-amino-4-oxobutanoic acid.

15 To a solution of 100 mg of N-(N-Acetyl-tyrosinyl-valinyl-pipocolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran in 10 ml of methanol was added 60 mg of Pd(OH)₂ on carbon and the mixture placed under an atmosphere of hydrogen via a balloon. The mixture was filtered through Celite and concentrated providing a white solid. This crude solid was dissolved in 2 ml of methanol and triturated with diethyl ether affording 26 mg of the title compound.

20 ¹H NMR (500 MHz, CD₃OD(existing as diastereomers as well as rotamers)) δ 7.1 (m, 2H), 6.7 (m, 2H), 5.2 (br. m, 1H), 4.8-3.6 (m, 6H), 3.2-2.5 (m, 4H), 2.5-2.1 (m, 1H), 1.95 (three s, 3H), 1.9-1.3 (m, 6H), 1.1-0.7 (m, 6H).

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K. N-[N-Acetyl-tyrosinyl-valinyl-(4-
benzyloxy)prolinyl]-3-amino-4-oxobutanoic acid.

Step A. N-(N-Allyloxycarbonyl-4-
benzyloxyprolinyl)-3-amino-4-oxobutanoic
5 acid tert-butyl ester semicarbazone.

The title compound was prepared by the reaction of N-allyloxycarbonyl-4-benzyloxyproline and 3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (T.L. Graybill et. al., Abstracts of 10 papers, 206th National Meeting of the American Chemical Society, Abstract MEDI-235. Chicago, IL. (1993)) under similar peptide coupling conditions as reported above (compound H; Step C).

15 ^1H NMR (500 MHz, CDCl_3) δ 9.05 (br. s, 1H),
7.85 (br. m, 1H), 7.4-7.2 (m, 5H), 7.15 (br. s, 1H),
6.55 (br. s, 1H), 5.9 (m, 1H), 5.1-4.9 (br. m, 2H),
4.65-4.4 (m, 4H), 4.2 (br. m, 1H), 3.75-3.5 (m, 2H),
2.75-2.55 (m, 2H), 2.5 (br. m, 1H), 2.25 (br. m, 1H)
1.4 (s, 9H).

20 Step B. N-(N-Acetyl-tyrosinyl-valinyl-(4-
benzyloxyprolinyl))-3-amino-4-oxobutanoic
acid tert-butyl ester semicarbazone.

The title compound was prepared by reaction of N-acetyl-tyrosinyl-valine and N-(N-allyloxycarbonyl-4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone by reaction conditions reported for compound H, step A.

25 ^1H NMR (500MHz, CD_3OD) δ 7.35-7.2 (m, 6H), 7.0 (d, 2H), 6.65(d, 2H), 4.85 (m, 1H), 4.6-4.45 (m, 4H),
30 4.3 (br. m, 1H), 4.15 (m, 1H), 3.7 (m, 1H), 2.95 (m,

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IH), 2.75-2.6 (m, 3H), 2.35 (m, 1H), 2.1 (m, 1H), 1.9 (s, 3H), 1.4 (s, 9H), 0.95 (d, 3H), 0.90 (s, 3H).

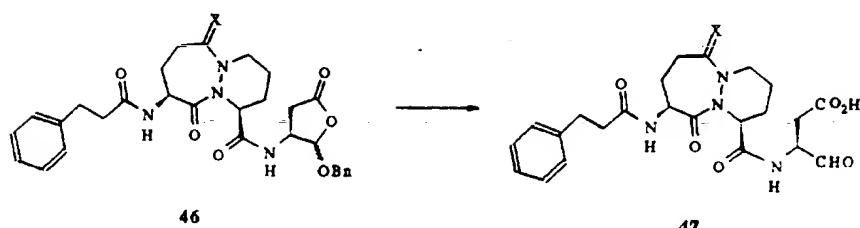
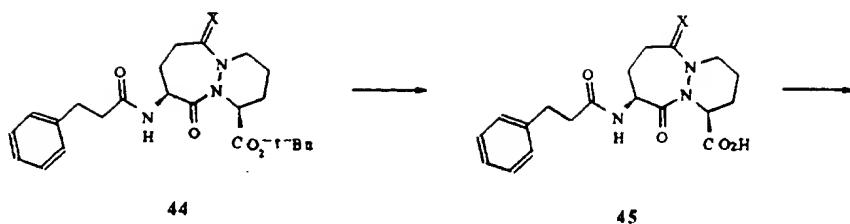
Step C. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid.

5

N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (270 mg) was dissolved into 10 ml of 25% trifluoroacetic acid in dichloromethane 10 and stirred at room temperature for 3 hours. The mixture was concentrated to give a solid residue. The residue was dissolved into a 10 ml mixture of methanol:acetic acid:37% formaldehyde (3:1:1) and stirred at room temperature for 1 hour. The mixture 15 was concentrated and the resulting residue purified by flash chromatography (SiO_2) eluting with dichloromethane/methanol/formic acid (100:5:0.5) to give 37 mg of the title compound.

^1H NMR (500 MHz, CD_3OD (existing as a 1:1 20 mixture of diastereomers of the hemiacetal)) δ 7.4-7.25 (m, 5H), 7.0 (d, 2H), 6.65 (d, 2H), 4.65-4.05 (m, 7H), 3.75-3.4 (m, 2H), 3.05-2.3 (m, 5H), 2.2-1.95 (m, 2H), 1.90 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).

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(a) X = O

(b) X = H₂

(1*S*,9*S*) t-Butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6*H*-pyridazino[1,2-a]

- 5 [1,2]diazepine-1-carboxylate (**44a**). To a solution of (1*S*,9*S*)t-butyl 9-amino-6,10-dioxo-octahydro-6*H*-pyridazino [1,2-a][1,2]diazepine-1-carboxylate (690mg; 2.32mmol; GB 2128984) in dioxane (16ml) and water (4ml) at 0°C was added solid sodium bicarbonate (292mg; 3.48mmol) followed by dropwise addition of 3-phenylpropionyl chloride (470mg; 2.78mmol). The mixture was stirred at room temperature for 2h then more sodium bicarbonate (200mg; 2.38mmol) and 3-phenylpropionyl chloride (100mg; 0.6mmol) were added.
- 10 The mixture was stirred for a further 2h at room temperature, diluted with ethyl acetate (50ml), washed with saturated sodium bicarbonate (2 x 25ml) then dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (0-50% ethyl acetate/chloroform)
- 15

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and finally crystallized by trituration with ether to afford 860mg (86%) of a white solid: mp. 137-138°C; $[\alpha]_D^{23}$ -95.1° (c 0.549, CH₂Cl₂); IR (KBr) 3327, 1736, 1677, 1664, 1536, 1422, 1156; ¹H NMR (CDCl₃) δ 7.24

5 (5H, m), 6.50 (1H, d, J=7.5), 5.24 (1H, m), 4.90 (1H, m), 4.60 (1H, m), 3.44 (1H, m), 2.93 (2H, m), 2.84 (1H, m), 2.64 (1H, m), 2.54 (2H, m), 2.26 (2H, m), 1.70 (4H, m), 1.70 (9H, s). MS(FAB, m/z): 430 (M⁺ + 1), 374, 242, 105, 91.

10 **(1S,9S) t-Butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a]
[1,2]diazepine-1-carboxylate (44b)**, was prepared from (1S,9S) t-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (Attwood et al., *J. Chem. Soc. Perkin 1*, pp. 1011-19 (1986)) as for **44a**, to afford 810mg (81%) of a colorless oil: $[\alpha]_D^{23}$ - 33.5° (c 0.545, CH₂Cl₂); IR (film) 3334, 2935, 1737, 1728, 1659, 1642; ¹H NMR (CDCl₃) δ 7.24 (5H, m), 6.75 (1H, d, J=6.7), 5.27 (1H, m), 4.92 (1H, m), 3.39 (1H, m), 3.03 (4H, m), 2.55 (3H, m), 2.33 (1H, m), 2.17 (1H, m), 1.80 (5H, m), 1.47 (9H, s), 1.39 (1H, m). MS(FAB, m/z): 416 (M⁺ + 1), 360, 211, 143, 97.

(1S,9S) 6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]

25 **[1,2]diazepine-1-carboxylic acid (45a)**. To a solution of (1S,9S) t-butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44a) (800mg; 1.863mmol) in dry dichloromethane (5ml) at 0°C was added 30 trifluoroacetic acid (5ml). The solution was stirred at room temperature for 3h then concentrated. Dry

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ether (10ml) was added to the residue then removed under vacuum. This process was repeated three times to afford a crystalline solid. The solid was triturated with ether and filtered to afford 590mg (85%) of a
5 white crystalline solid: mp. 196-197.5°C; $[\alpha]_D^{23}$ -129.5°
(c 0.2, CH₃OH); IR (KBr) 3237, 1729, 1688, 1660, 1633,
1574, 1432, 1285, 1205; ¹H NMR (CD₃OD) δ 8.28 (1H, d,
J=7.4), 7.22 (5H, m), 5.32 (1H, dd, J=5.9, 2.9), 4.75
(1H, m), 4.51 (1H, m), 3.50 (1H, m), 3.01 (1H, m), 2.91
10 (2H, m), -2.55 (2H, m), 2.29 (3H, m), 1.95 (2H, m), 1.71
(2H, m). Anal. Calcd for C₁₉H₂₃N₃O₅: C, 61.12; H, 6.21;
N, 11.25. Found: C, 60.80; H, 6.28; N, 10.97. MS(FAB,
m/z) 374 (M⁺ + 1), 242, 105, 91.

(1*S*,9*S*) Octahydro-10-oxo-9-(3-phenylpropionylamino)-6*H*-
15 pyridazino[1,2-a]-[1,2]diazepine-1-carboxylic acid
(45b), was prepared from (1*S*,9*S*) t-butyl octahydro-10-
oxo-9-(3-phenylpropionylamino)-6*H*-
pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44b) by
the method described for compound 45a to afford 657mg
20 (96%) of 45b as a crystalline solid: mp. 198-202°C;
 $[\alpha]_D^{23}$ -86.2° (c 0.5, CH₃OH); IR (KBr) 3294, 2939, 1729,
1645, 1620, 1574, 1453, 1214; ¹H NMR (CD₃OD) δ 7.92
(1H, d, J=7.9), 7.20 (5H, m), 5.29 (1H, m), 4.90 (1H,
m), 3.47 (1H, m), 3.08 (2H, m), 2.90 (2H, m), 2.55 (3H,
m), 2.36 (1H, m), 1.81 (5H, m), 1.43 (2H, m). MS(FAB,
25 m/z) 360 (M⁺ + 1), 211, 143, 91.

[3*S*,2*R*,*S*,(1*S*,9*S*)] N-(2-Benzylxy-5-oxotetrahydrofuran-
3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-
6*H*-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46a).
30 To a solution of (1*S*,9*S*) 6,10-dioxo-octahydro-9-(3-
phenyl-propionylamino)-6*H*-pyridazino[1,2-a]

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[1,2]diazepine-1-carboxylic acid (**45a**) (662mg; 1.773mmol) in dry dichloromethane (9ml) and dry dimethyl formamide (3ml) at room temperature was added bis(triphenylphosphine)palladium chloride (30mg) and
5 (3*S*,2*R*,*S*)-3-allyloxycarbonylamino-2-benzylxy-5-oxotetrahydrofuran (Chapman, Bioorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) (568mg; 1.95mmol) followed by dropwise addition of tri-n-butyltin hydride (1.19g; 4.09mmol). 1-Hydroxy-benzotriazole (479mg; 3.546mmol)
10 was added to the mixture and the mixture was cooled to 0°C before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (408mg; 2.128mmol). The mixture was stirred at room temperature for 3.25h then diluted with ethyl acetate (50ml), washed twice
15 with dilute hydrochloric acid (20ml), twice with saturated sodium bicarbonate (20ml), once with brine then dried (MgSO₄) and concentrated. The resulting oil was purified by flash chromatography (0-100% ethyl acetate/chloroform) to afford 810mg (81%) of **46a** as a
20 mixture of anomers: mp. 92-94°C; IR (KBr) 3311, 1791, 1659, 1651, 1536; ¹H NMR (CDCl₃) δ 7.49, 6.56 (1H, 2d, J=6.7, 7.8), 7.29 (10H, m), 6.37, 6.18 (1H, 2d, J=7.7, 7.6), 5.56, 5.34 (1H, d, s, J=5.2), 5.08-4.47 (6H), 3.18-2.80 (5H), 2.62-2.28 (5H), 2.04-1.53 (5H).
25 MS (FAB, m/z), 563 (M⁺ + 1), 328, 149, 91.

[3*S*,2*R*,*S*,(1*S*,9*S*)] N-(2-Benzylxy-5-oxotetrahydrofuran-3-yl)-octahydro-10-oxo-9-(3-phenylpropionylamino)-6*H*-pyridazino[1,2-a]
[1,2]diazepine-1-carboxamide (**46b**), was prepared from
30 **45b** by the method described for **46a** to yield 790mg (96%) of a glass: m.p. 58-60°C; IR (KBr) 3316, 2940, 1793, 1678, 1641, 1523, 1453, 1120; ¹H NMR (CDCl₃) δ

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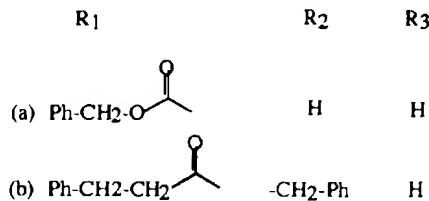
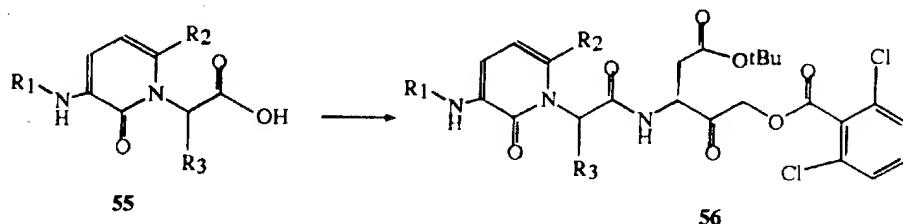
7.28 (10H, m), 6.52, 6.42 (1H, 2d, $J=7.2, 7.1$), 5.53, 5.44 (1H, d, s, $J=5.2$), 5.35 (1H, m), 4.6-4.9, 4.34 (4H, m), 3.1-2.8 (6H, m), 2.6-2.1 (7H), 1.95-1.05 (5H). MS(FAB, m/z), 549 ($M^+ + 1$), 400, 310, 279, 91.

- 5 [3S(1S,9S)] 3-(6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]
[1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47a). A mixture of [3S, 2R,S, (1S,9S)] N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]
[1,2]diazepine-1-carboxamide (46a) (205mg; 0.364mmol), 10% palladium on carbon (200mg) and methanol (20ml) was stirred under hydrogen at atmospheric pressure for 5h. The mixture was filtered then concentrated to yield 154mg (90%) of a glass: mp. 116-118°C; $[\alpha]_D^{23} -140^\circ$ (c 0.1, CH₃OH); IR (KBr) 3323 (br), 1783, 1731, 1658, 1539, 1455, 1425; ¹H NMR (CD₃OD) δ 7.21 (5H, m), 5.17 (1H, m), 4.73 (1H, m), 4.50 (2H, m), 4.23 (1H, m), 3.38 (1H, m), 3.06 (1H, m), 2.91 (2H, m), 2.73-2.18 (6H, m) and 2.01-1.59 (5H, m). Anal. Calcd for C₂₃H₂₇N₄O₇ + H₂O : C, 56.32; H, 6.16; N, 11.42. Found: C, 56.29; H, 6.11; N, 11.25. MS(FAB, m/z) 473 ($M^+ + 1$), 176, 149, 105, 91.

- [3S(1S,9S)]3-(Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a]
[1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47b), was prepared from 46b by the method described for 47a. The residue was purified by flash chromatography (0-10% methanol/chloroform) to afford 65mg (52%) of a glass; 30 m.p. 87-90°C; $[\alpha]_D^{23} -167.0^\circ$ (c 0.1, methanol); IR (KBr) 3329, 2936, 1786, 1727, 1637; ¹H NMR (CD₃OD) δ

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7.23 (5H, m), 5.29 (1H, m), 4.83 (1H, m), 4.59 (1H, d, J=3.6), 4.29 (1H, m), 3.3-3.0 (3H, m), 2.91 (2H, m), 2.70-2.34 (5H, m), 2.19 (2H, m), 1.75 (4H, m), 1.36 (2H, m). Anal. Calcd for C₂₃H₃₀N₄O₆ + 0.5H₂O: C, 59.09; H, 6.68; N, 11.98. Found: C, 58.97; 6.68; N, 11.73. MS(FAB, m/z) 459 (M⁺ + 1), 310, 149, 105, 91.



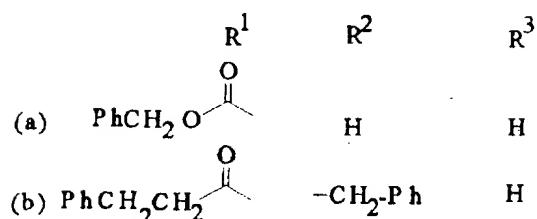
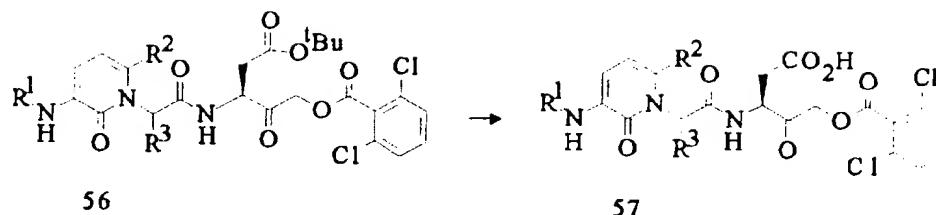
t-Butyl N-2-(3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoate (56a). The acetic acid (55a) (WO 93 21213) in THF (2ml) was stirred at room temperature and treated with 1-hydroxybenzotriazole (60mg, 0.448mmol) and dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (47mg, 0.246mmol). After 5 mins water (2 drops) was added and stirring continued for 20 minutes. Bis(triphenylphosphine) palladium II chloride (6mg) was added followed by a solution of t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyloxy)pentanoate (WO 93 16710) (103mg, 0.224mmol) in THF (1ml). Tributyltin hydride

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(0.09ml, 0.336mmol) was added dropwise over 1 hour at room temperature. The mixture was stirred for a further 3 hours and poured onto ethyl acetate, washed with 1M HCl, aqueous NaHCO₃, brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was triturated with pentane and the supernatant discarded. The remaining solid was purified by flash chromatography (50% ethyl acetate/hexane) to afford the title compound 92mg (63%) as a colorless oil: [α]_D²⁶ -29.6° (c 1.1, CH₂Cl₂); IR (film) 3377, 3365, 3332, 3312, 1733, 1691, 1650, 1599, 1515, 1366, 1261, 1153, 1068, 747; ¹H NMR (CDCl₃) δ 8.09 (1H, d, J = 6.8), 7.84 (1H, s), 7.58 (1H, d, J = 8.3), 7.33 (8H, m), 7.02 (1H, dd, J = 6.9, 1.7), 6.33 (1H, t, J = 7.2), 5.20 (2H, s), 5.12 (2H, m), 4.89 (1H, dt), 4.65 (2H, m), 2.80 (2H, m), 1.38 (9H, s).

t-Butyl N-2-(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzylxy)-4-oxo-pentanoate (56b), was prepared 20 by the method described for (56a) which afforded the title compound (66%) as a colorless oil: IR (film) 3364, 3313, 1738, 1688, 1648, 1600, 1566, 1514, 1433, 1369, 1254, 1152; ¹H NMR (CDCl₃) δ 8.40 (1H, d, J 7.6), 8.30 (1H, s), 7.28 (13H, m), 6.20 (1H, d, J = 7.6), 5.12 (2H, q), 4.86 (1H, m), 4.65 (2H, q), 4.06 (2H, s), 3.07-2.61 (6H, m), 1.39 (9H, s).

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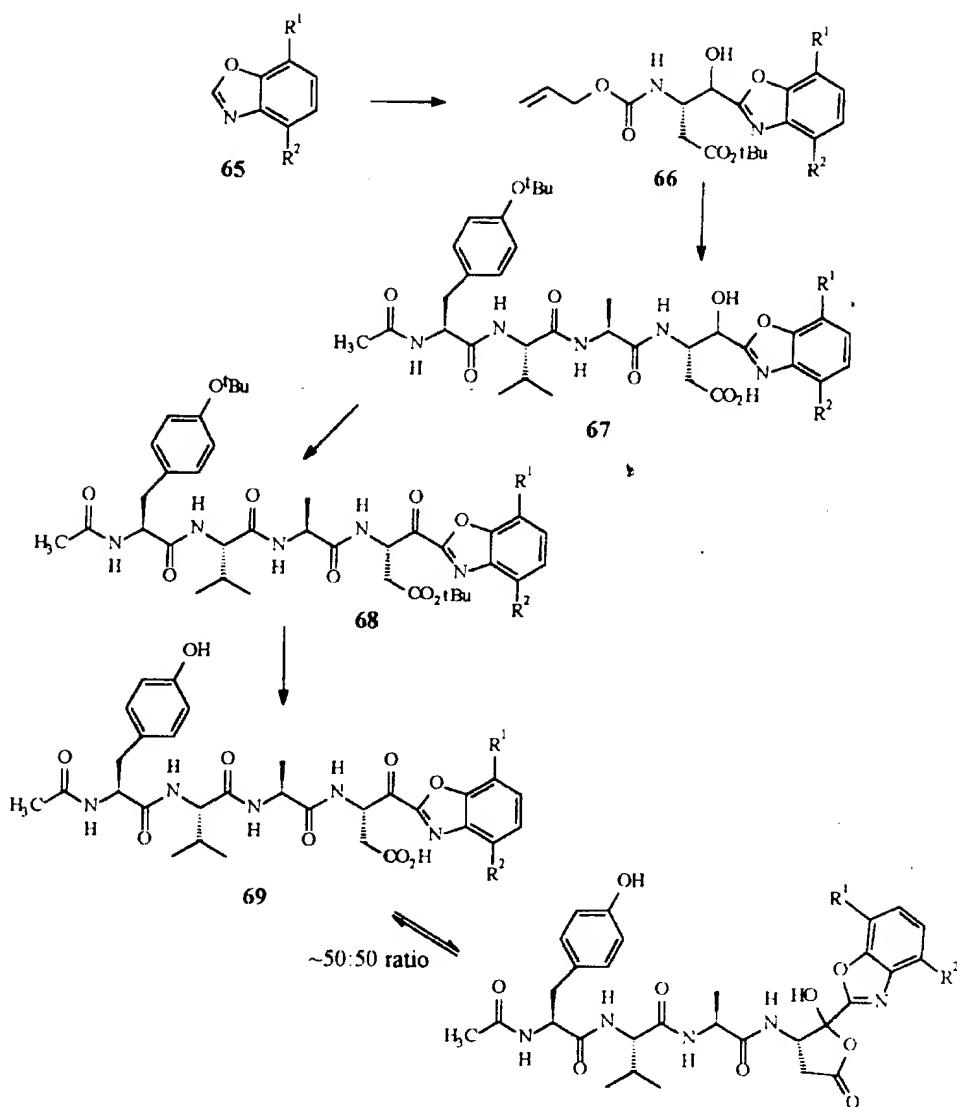


N-2(3-Benzylxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57a; Q). The ester 56a (210mg, 0.356mmol) in dichloromethane (0.5ml) was cooled to 0°C and treated with trifluoroacetic acid (0.5ml), stirred and warmed to 20°C over 30 minutes. The solution was evaporated to dryness under reduced pressure, redissolved in dichloromethane and concentrated (x3). The residue was triturated with ethyl acetate and diluted with ether to afford the title compound 162mg (85%) as a colorless solid: m.p. 165-8°C (decomposition); $[\alpha]_D^{23} -38.8^\circ$ (c 0.1, CH₃OH); IR (KBr) 3332, 3275, 1723, 1658, 1649, 1597, 1581, 1562, 1526, 1432, 1385, 1258, 1218, 1206; ¹H NMR (δ_6 -DMSO) δ 8.96 (1H, d, $J = 7.3$), 8.34 (1H, s), 7.85 (1H, dd, $J = 7.3$), 7.58 (3H, m), 7.35 (5H, m), 6.29 (1H, t, $J = 7.3$), 5.26 (2H, m), 5.15 (2H, s), 4.69 (3H, m), 2.75 (2H, m). Anal. Calcd. C₂₇H₂₃N₃O₉Cl₂: C, 53.66; H, 3.84; N, 6.95. Found: C, 53.36; H, 3.90; N, 6.81. M.S. (+ FAB); 604 ($M^+ + 1$), 285, 241, 195, 173, 149, 91.

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N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57b; P), was prepared by the method described for 57a which afforded the title compound (78%) as colorless crystals: m.p. 116-120°C (decomposition); $[\alpha]_D^{26} -41.1^\circ$ (c 0.1, CH₃OH); IR (KBr) 3299, 1739, 1715, 1689, 1666, 1645, 1598, 1563, 1518, 1432, 1209, 1151; ¹H NMR (d₆-DMSO) δ 9.24 (1H, s), 8.88 (1H, d, J = 7.6), 8.18 (1H, d, J = 7.7), 7.60 (3H, m), 7.26 (10H, m), 6.06 (1H, d, J = 7.7), 5.23 (2H, ABq), 4.69 (3H, m), 3.93 (2H, s), 2.78 (6H, m). Anal. Calcd. for C₃₅H₃₁N₃O₈Cl₂. H₂O: C, 59.16; H, 4.68; N, 5.91. Found: C, 59.38; H, 4.53; N, 5.84. M.S. (+ FAB); 694, (Cl=35, 37), (M⁺ + 1); 692 (Cl=35, 35), (M⁺ + 1).

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(a) R¹ = OCH₃, R² = H(b) R¹ = H, R² = OCH₃

7-Methoxybenzoxazole (65a). A mixture of 2-nitro-6-methoxyphenol (2.62g, 15.5mmol) (EP 333176) and 10% Palladium on carbon (130mg) in ethanol (50.0ml) was stirred under an atmosphere of H₂ for 75min. The

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mixture was filtered through Celite® then immediately treated with *p*-toluenesulphonic acid (32.0mg) and triethylorthoformate (6.45ml, 38.8mmol) then heated under reflux under an atmosphere of N₂. After 20h *p*-toluenesulphonic acid (30.0mg) and triethylorthoformate (6.45ml, 38.8mmol) were added. After a total of 44h heating, the reaction was allowed to cool and reduced *in vacuo*. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give

10 1.97g (85%) of the title compound as a yellow solid: m.p. 28-31°C; IR (film) 1629, 1497, 1434, 1285, 1097; ¹H NMR (CDCl₃) δ 8.09 (1H, s), 7.40 (1H, d, J = 8.0), 7.28 (1H, t, J = 8.0), 6.89 (1H, d, J = 8.0), 4.02 (3H, s); ¹³C NMR (CDCl₃) δ 152.84, 145.82, 142.50, 139.99, 15 125.75, 113.42, 108.80, 56.97. Anal. Calcd. for C₈H₇N₁O₂. 0.1H₂O: C, 63.65; H, 4.81; N, 9.29. Found: C, 63.43, H, 4.88, N, 9.05. M.S. (+ FAB); 150 (M⁺ + 1).

4-Methoxybenzoxazole (65b). To a suspension of 4-hydroxybenzoxazole (2.00g, 14.8mmol) (Musser et al., J. Med. Chem., 30, pp. 62-67 (1987)) in acetone (80.0ml) was added dried K₂CO₃ (2.25g, 16.3mmol) followed by iodomethane (1.38ml, 22.2mmol). The reaction was heated under reflux under N₂ for 4.5h, then filtered and reduced *in vacuo* to afford the crude product. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 2.0g (91%) of the title compound as a white crystalline solid: m.p. 72-74°C; IR (KBr) 3089, 1619, 1610, 1503, 1496, 1322, 1275, 1090, 1071, 780, 741; ¹H NMR (CDCl₃) δ 8.02 (1H, s), 7.32 (1H, t, J = 8.0), 7.18 (1H, d, J = 8.0), 6.81 (1H, d, J = 8.0), 4.04 (3H, s). Anal. Calcd. for

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C₈H₇NO₂: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.84; N, 9.31; m/z (EI) 149 (M⁺ + 1, 100%).

(3*S*, 4*R,S*) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (66a).

- 5 To a stirred solution of 7-methoxybenzoxazole 65a (548.6mg, 3.68mmol) in anhydrous THF (18.5ml) at -78°C under N₂ was added 1.56M n-butyl lithium in hexanes (2.47ml, 3.86mmol) dropwise, to produce a yellow colored solution. After stirring at -78°C for 20 min, ~ 10 dry MgBr₂OEt₂ (1.045g, 4.05mmol) was added as a solid. The resulting heterogeneous mixture was warmed to -45°C and stirred for 15min. The reaction mixture was then recooled to -78°C and a solution of (S)-Alloc-Asp(t-Bu)H (946.4mg, 3.68mmol) in THF (18.5ml) was added 15 dropwise. The reaction was stirred at -78°C for 30min, warmed to 0°C and stirred for 1h. The resulting homogeneous reaction was warmed to room temperature and stirred for 16h. The reaction was quenched with 5% sodium bicarbonate (3.5ml) then THF was removed *in vacuo*. The resulting aqueous residue was extracted with methylene chloride (x6). The combined extracts were washed with brine, dried (MgSO₄), filtered and reduced *in vacuo* to give 1.8g of crude product. Flash chromatography (40:60 ethyl acetate/hexane) gave 1.21g 20 (81%) of the title compound, an oil, as a mixture of diastereoisomers at C-4: IR (CH₂Cl₂) 3425, 2983, 1725, 1504, 1290, 1157, 1101; ¹H NMR (CDCl₃) δ 7.35-7.19 (2H, m), 6.89-6.81 (1H, m), 6.00-5.57 (2H, m), 5.32-5.05 (3H, m), 4.68-4.35 (3H, m), 4.01 (3H, s), 2.86-2.59 (2H, m), 1.45 (9H, s), 1.41 (9H, s); ¹³C NMR (CDCl₃) δ 171.18, 171.09, 165.80, 165.30, 156.71, 156.60, 145.65, 142.76, 142.71, 140.82, 140.72, 133.23, 125.81, 125.72,

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118.41, 118.21, 113.07, 112.87, 108.95, 82.16, 70.28,
69.98, 66.52, 66.39, 57.03, 52.57, 52.29, 37.83, 36.86,
28.65. Anal. Calcd. for C₂₀H₂₆N₂O₇. 0.6H₂O: C, 57.57;
H, 6.57; N, 6.72. Found: C, 57.49, H, 6.34, N, 6.60.
5 M.S. (+ FAB); 407 (M⁺ + 1); 351, 307, 154.

(3*S*, 4*R,S*) *t*-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (66b), was prepared according to the method described for 66a which afforded 1.29g (26%, 68% based on recovered

10 starting material) of the title compound as an oil and as a mixture of diastereoisomers at C-4: IR (CH₂Cl₂) 3400, 1725, 1625, 1505, 1369, 1354, 1281, 1263, 1226, 1158, 1092, 1048; ¹H NMR (CDCl₃) δ 7.34-7.24 (1H, m), 7.16 (1H, d, J = 8.2), 6.79 (1H, d, J = 7.9), 6.00-5.50
15 (2H, m), 5.30-5.05 (3H, m), 4.70-4.35 (4H, m), 4.02 (3H, s), 2.90-2.45 (2H, m), 1.45-1.41 (9H, 2 x s).
Anal. Calcd. for C₂₀H₂₆N₂O₇. 0.4H₂O: C, 58.07; H, 6.53; N, 6.77. Found: C, 58.09; H, 6.41; N, 6.63.
M.S. (+ FAB); 407 (M⁺ + 1, 88%); 351 (100).

20 (3*S*, 4*R,S*) *t*-Butyl N-(N-acetyl-(*S*)-(O-*tert*-butyl-tyrosinyl)-(S)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (67a). To a stirred solution of the benzoxazole 66a (481.9mg, 1.19mmol) and Ac-Tyr(^tBu)-Val-Ala-OH (586.3mg, 1.30mmol) in methylene chloride (3.5ml) and DMF (3.5ml) was added bis(triphenylphosphine) palladium (II) chloride (18.0mg), followed by tributyltinhydride (0.80ml, 2.96mmol) dropwise. Hydroxybenzotriazole (320.4mg, 2.37mmol) was added and the mixture cooled to
25 0°C. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (278.2mg, 1.42mmol) was added and the

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mixture was allowed to warm to room temperature and stirred for 16.5h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, water, and brine. The organic layer was dried ($MgSO_4$), filtered and reduced *in vacuo* to yield 2.0g of crude product. Flash chromatography (95:5 methylene chloride/methanol) gave 844.0mg (94%) of the title compound as a white solid: m.p. 205°C; IR (KBr)

10 3399, 3304, 2977, 1729, 1643, 1506, 1367, 1290, 1161; 1H NMR (d_6 -DMSO) δ 8.24-7.78 (4H, m), 7.43-7.32 (2H, m), 7.23 (2H, d, J = 8.5), 7.16-7.07 (1H, m), 6.93 (2H, d, J = 8.5), 6.52, 6.40 (1H, 2 x d, J = 5.5, J = 5.0), 5.03, 4.78-4.49, 4.45-4.16 (5H, brt, 2 x m), 4.05, 4.04 (3H, 2 x s), 3.08-2.35 (14H, m), 2.11-1.89 (1H, m), 1.83 (3H, s), 1.49-1.32, 1.15, 1.0-0.81 (27H, s, 2 x m, J = 7.0); ^{13}C NMR (d_6 -DMSO) δ 175.55, 175.18, 173.88, 173.75, 173.05, 169.23, 157.28, 148.55, 146.16, 143.21, 136.63, 133.55, 128.87, 127.17, 115.78, 111.92, 84.02,

15 20 81.50, 71.40, 61.15, 60.05, 57.79, 53.39, 51.62, 43.76, 40.52, 34.58, 32.52, 31.60, 26.35, 23.11, 22.71, 21.76. Anal. Calcd. for $C_{39}H_{55}N_5O_{10}$. 0.5H₂O: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.43; H, 7.31; N, 9.07. M.S. (+ FAB); 754 ($M^+ + 1$); 698, 338, 267.

25 30 (3*S*, 4*R,S*) *t*-Butyl N-(*N*-acetyl-(*S*)-(O-*tert*-butyl-tyrosinyl)-(S)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (67b), was prepared according to the method described for 67a which afforded 1.05g (94%) of the title compound as a fine white powder: m.p. 210-213°C (dec); IR (KBr) 3284, 2977, 1736, 1691, 1632, 1536, 1505, 1452, 1392, 1367, 1258, 1236, 1161, 1091; 1H NMR (d_6 -DMSO) δ 8.20-

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7.75 (4H, m), 7.40-7.10 (4H, m), 7.00-6.80 (3H, m),
6.45, 6.34 (1H, 2 x d, $J = 5.3$, $J = 5.0$), 5.00-4.10
(5H, m), 4.00, 3.99 (3H, 2 x s), 3.00-2.25 (4H, m),
1.95 (1H, m), 1.78 (3H, s), 1.39-0.80 (27H, m). Anal.
5 Calcd. for $C_{39}H_{55}N_5O_{10}$. 0.5H₂O: C, 61.40; H, 7.40; N,
9.18. Found: C, 61.58; H, 7.38; N, 8.91. M.S.
(+ FAB); 754 ($M^+ + 1$, 30%); 72 (100).

**(3S) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-
(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-**
10 **methoxybenzoxazolyl))-4-oxobutanoate (68a)**. The Dess-
Martin reagent (1.082g, 2.55mmol) (Ireland et al., J.
Org. Chem., 58, p. 2899 (1993); Dess et al., J. Org.
Chem., 48, pp. 4155-4156 (1983)) was added to a stirred
suspension of the alcohol **67a** (641.0mg, 0.85mmol) in
15 methylene chloride (46.0ml). The resulting mixture was
stirred for 1h before being partitioned between
saturated sodium thiosulphate: saturated sodium
bicarbonate (1:1, 86.0ml) and ethyl acetate (86.0ml).
The resultant organic phase was washed in turn with
20 saturated sodium thiosulphate: saturated sodium
bicarbonate (1:1), saturated sodium bicarbonate, and
brine. The organic phase was dried ($MgSO_4$), filtered
and reduced *in vacuo* to give 660.0mg of crude product.
Flash chromatography (94:6 methylene chloride/methanol)
25 gave 636.0mg (100%) of the title compound as a white
solid: m.p. 209°C; $[\alpha]_D^{24} -21.6^\circ$ (c 0.16, methanol); IR
(KBr) 3395, 3294, 2977, 1722, 1641, 1535, 1505, 1161;
¹H NMR ($CDCl_3$) δ 8.43-8.16 (1H, m), 7.97-7.62 (2H, m),
7.49-7.14 (3H, m), 7.08-6.95 (3H, m), 6.89-6.73 (2H,
30 m), 5.81-5.68 (1H, m), 5.16-4.86 (2H, m), 4.53 (1H,
brt), 4.03 (3H, s), 3.16-2.84 (4H, m), 2.11-1.84 (4H,
m), 1.46-1.14 (21H, m), 0.92-0.78 (6H, m); ¹³C NMR

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(CDCl₃) δ 186.28, 173.39, 171.90, 171.19, 171.03,
169.89, 156.43, 154.75, 146.32, 142.88, 140.98, 132.31,
130.54, 126.98, 124.73, 114.95, 111.42, 82.44, 78.71,
58.92, 57.20, 54.91, 53.47, 48.77, 39.43, 38.15, 32.79,
5 29.44, 28.60, 23.55, 20.27, 19.70, 19.34. M.S.
(+ FAB); 752 (M⁺ + 1); 696, 336, 265.

(3S) t-Butyl N-(N-acetyl-(S)-(O)-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (68b), was
10 prepared according to the method described for the ketone **68a** which afforded 420mg (55%) of the title compound as a white solid: m.p. 211-213°C (dec); [α]_D²⁴ -23.9° (c 0.82, methanol); IR (KBr) 3277, 3075, 1723, 1690, 1632, 1530, 1506, 1392, 1366, 1269, 1234, 1160, 15 1094; ¹H NMR (CDCl₃) δ 8.15 (1H, brs), 7.7 (2H, brs), 7.46 (1H, t, J = 8.3), 7.24 (2H, d, J = 8.3), 7.10 (1H, brs), 7.03 (2H, d, J = 8.3), 6.83 (3H, m), 5.74 (1H, q, J = 6.9), 5.00 (2H, m), 4.51 (1H, t, J = 7.0), 4.07 (3H, s), 3.20-2.95 (4H, m), 2.00 (4H, m), 1.42 (3H, d, J = 6.8), 1.35 (9H, s), 1.23 (9H, s), 0.86 (6H, d, J = 6.7). M.S. (+ FAB); 752 (M⁺ + 1, 7%); 72 (100).

(3S) N-(N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (69a; R). A solution of the ester **68a** (600.0mg, 0.80mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (65.0ml) was stirred for 1h under a dry atmosphere of N₂. The solution was then reduced *in vacuo*, taken up in ether and reduced again. This process was repeated six times to afford 25 the crude product as an off white solid. Flash chromatography (gradient 95:5 to 80:20 methylene 30 chloride/ether) afforded 100mg (15%) of the title compound.

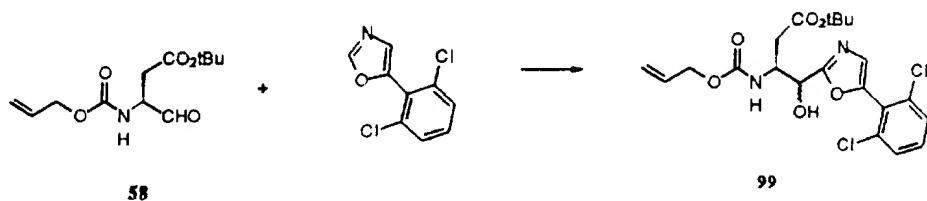
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chloride/methanol) gave 420.8mg (83%) of the title compound as a hygroscopic white solid. The product existed as a mixture of three isomers in CD₃OD, consisting of the keto form (c 50%), and its acycloxy 5 keto form (two isomers at C-4, c 50%): m.p. decomposes above 150°C; $[\alpha]_D^{24}$ -33.2° (c 0.17, methanol); IR (KBr) 3300, 1715, 1658, 1650, 1531, 1517, 1204; ¹H NMR (CD₃OD) δ 7.46-7.19 (2H, m), 7.16-6.91 (3H, m), 6.70- 10 6.59 (2H, m), 5.62-5.49 (1H, m), 5.00-4.72 (1H, obscured m), 4.69-4.51 (1H, m), 4.49-4.08 (2H, m), 4.05-3.89 (3H, m), 3.16-2.47 (4H, m), 2.05-1.78 (4H, m), 1.41-1.11, 1.05-0.70 (9H, 2 x m). Anal. Calcd. for C₃₁H₃₇N₅O₁₀. 3H₂O: C, 53.67; H, 6.25; N, 10.10. Found: C, 53.76; H, 5.56; N, 10.28. M.S. (+ FAB); 640 15 (M⁺ + 1); 435, 147.

(3S) t-Butyl N-(N-acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (69b; S), was prepared according to the method described for the acid 69a which afforded the 20 hygroscopic title compound 252mg (96%). The product existed as a mixture of three isomers in CD₃OD, consisting of the keto form, and its acycloxy ketal form (two isomers at C-4). The product existed as a single isomer in d-6 DMSO: m.p. 200-203°C (dec.); 25 $[\alpha]_D^{24}$ -38.0° (c 0.23, methanol); IR (KBr) 3289, 2968, 1718, 1713, 1658, 1634, 1548, 1517, 1506, 1461, 1453, 1393, 1369, 1268, 1228, 1174, 1092; ¹H NMR (d₆-DMSO) δ 9.20 (1H, brs), 8.71 (1H, d, J = 6.2), 8.10 (2H, m), 7.63 (1H, d, J = 8.7), 7.61 (1H, t, J = 8.2), 7.46 (1H, d, J = 8.2), 7.08 (3H, m), 6.65 (2H, d, J = 8.3), 5.50 (1H, q, J = 6.5), 4.50 (1H, m), 4.37 (1H, m), 4.29 (1H, m), 4.05 (3H, s), 3.09-2.77 (4H, m), 1.94 (1H, m), 1.79

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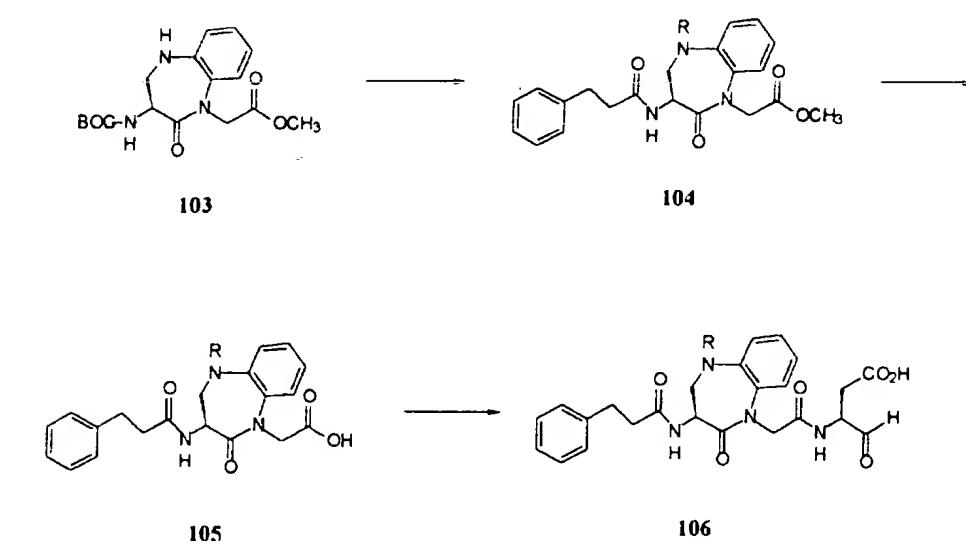
(3H, s), 1.23 (3H, d, $J = 7.0$), 0.82 (6H, m). Anal.
Calcd. for $C_{31}H_{37}N_5O_{10}$. 1.5 H_2O : C, 55.85; H, 6.05; N, 10.51. Found: C, 55.21; H, 5.69; N, 10.13. M.S.
(+ FAB); 640 ($M^+ + 1$, 22%); 107 (100).



5 **3(S)-{(Allyloxycarbonyl)-amino-4-[(2,6-dichlorophenyl)-oxazol-2-yl]-4(R,S)-hydroxy-butryic acid tert-butyl ester (99)}.** A solution of 5-(2,6-Dichlorophenyl)oxazole (2.71g, 12.7mmol; prepared by a similar method described in Tet. Lett. 23, p. 2369
10 (1972)) in tetrahydrofuran (65mL) was cooled to -78 °C under a nitrogen atmosphere. To this solution was added n-butyl lithium (1.5M solution in hexanes, 8.5mL, 13.3mmol) and stirred at -78 °C for 30min. Magnesium bromide etherate (3.6g, 13.9mmol) was added and the
15 solution was allowed to warm to -45 °C for 15min. The reaction was cooled to -78 °C and aldehyde 58 (3.26g, 12.7mmol; Graybill et al., Int. J. Protein Res., 44, pp. 173-182 (1993)) in tetrahydrofuran (65mL) was added dropwise. The reaction was stirred for 25min., then
20 allowed to warm to -40 °C and stirred for 3h, and then at room temperature for 1h. The reaction was quenched with 5% $NaHCO_3$ (12mL) and stirred for 3h. The tetrahydrofuran was removed in vacuo and the resulting residue was extracted with dichloromethane. The
25 organic layer was washed with saturated sodium chloride solution and dried over magnesium sulfate, filtered, and concentrated to yield 6.14g of the title compound.

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Purification gave 4.79g (80%) of **99**: ^1H NMR (CDCl_3) δ 1.45(s, 9H), 2.7-2.5(m, 2H), 2.8(dd, 1H), 4.2, 4.4(2 x d, 1H), 4.7-4.5(m, 3H), 5.35-5.1(m, 2H), 5.6, 5.7(2 x d, 1H), 6.0-5.8(m, 1H), 7.2(d, 1H), 7.3(m, 1H), 7.4(m, 5 2H).



a R = H

b R = $\text{COCH}_2\text{CH}_2\text{Ph}$

c R = CH_2Ph

- [2-Oxo-3(S)- (3-phenylpropionylamino)-2,3,4,5-
10 tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid
methyl ester (**104a**). Anhydrous hydrogen chloride was
bubbled into a solution of (3(S)-tert-
butyloxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-benzo[b];
[1,4]diazepin-1-yl)acetic acid methyl ester (**103**, 1g,
15 2.86 mmol) in 25 ml of ethyl acetate for 2 minutes then
stirred for 1 hour at room temperature. The reaction
was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-

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tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.

The hydrochloride salt and hydrocinnamic acid (0.47 g, 3.15 mmol) were dissolved into 20 ml of

5 dimethylformamide and cooled to 0 °C.

Diisopropylethylamine (1 ml, 5.72 mmol) was added to

the solution followed by the addition of N-

hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring for 18

10 hours at room temperature, the mixture was diluted with 150 ml of ethyl acetate and washed with 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and brine.

The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to a crude solid that

15 was purified by flash chromatography eluting with 7:3 ethyl acetate/dichloromethane to afford 600 mg (55%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ

7.3-6.85 (9H, m), 6.55-6.0 (1H, d), 4.88-4.82 (1H, m),

4.72-4.65 (1H, d), 4.28-4.22 (1H, m), 3.95-3.9 (1H, m),

20 3.78 (3H, s), 3.65 (1H, br. s), 3.28-3.2 (1H, m), 2.95-2.84 (2H, m), 2.55-2.4 (2H, m).

(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetra-

hydrobenzo[b][1,4]diazepin-1-yl)acetic acid (105a).

(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-

25 tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid

methyl ester (104a) was dissolved in 90% methanol.

Lithium hydroxide hydrate was added to the reaction and the reaction was stirred at room temperature for 4 h.

The reaction was evaporated in vacuo to give a white

30 solid. This was dissolved in 20 ml of water and

acidified to pH 5 and extracted with ethyl acetate to

afford 304 mg (88%) of the title compound as a white

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solid. ^1H NMR (CDCl_3) δ 7.5-6.9 (11H, m), 4.92-4.8 (1H, m), 4.7-4.58 (1H, d), 4.38-4.25 (1H, d), 3.88-3.78 (1H, m), 3.45-3.25 (1H, m), 3.05-2.85 (2H, m), 2.55-2.45 (2H, m).

5 **4-Oxo-3(S)-{2-[2-oxo-3(S)-(3-phenylpropionylamino)-
2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-
ylacetylamino]butyric acid (106a).** N-(1-(2-Benzyloxy-
5-oxotetrahydrofuran-3-ylcarbamoyl-methyl)-2-oxo-
2,3,4,5-tetrahydro-1H-benz[b][1,4]diazepin-3-yl)-3-
10 phenylpropionamide was prepared from **105a** by the
procedure used to prepare compound **H** (stepA) to afford
390 mg (93%) of the product as diastereomers. ^1H NMR
(CD_3OD) δ 7.58-7.22 (14H, m), 5.78-5.73 (0.5 H, d), 5.64
(0.5 H, s), 5.0-4.72 (4H, m), 4.54-4.42 (2H, m), 3.82-
15 3.76 (0.5 H, m), 3.68-3.62 (0.5 H, m), 3.28-3.21 (0.5H,
m), 3.19-3.12 (0.5H, m), 3.07-2.98 (2H, m), 2.76-2.48
(4H, m).

The resulting product was converted to **106a** by the
method described to prepare compound **H** (StepD) to
20 afford the title compound as a white solid (17%): ^1H
NMR (CD_3OD) δ 7.54-6.98 (9H, m), 5.58-5.44 (1H, m), 4.8-
4.2 (4H, m), 3.96-3.3 (2H, m), 3.30-3.05 (1H, m), 2.98-
2.25 (5H, m).

25 **[2-Oxo-5-(3-phenylpropionyl)-3(S)-(3-
phenylpropionylamino)-2,3,4,5-
tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl
ester (104b).** Anhydrous hydrogen chloride was bubbled
into a solution of (3(S)-tert-butoxycarbonylamino-2-
oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-
30 yl)acetic acid methyl ester (**103**, 1g, 2.86mmol) in 25

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ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.

The hydrochloride salt was suspended into 20 ml of dichloromethane and cooled to 0 °C. Triethylamine (1.6 ml, 11.5 mmol) was added to the suspension followed by the dropwise addition of dihydrocinnamoyl chloride (0.9 ml, 6 mmol). The mixture was warmed to room temperature and stirred for 18 hours. The mixture was diluted with 25 ml of dichloromethane and washed twice with 50 ml of water and once with 50 ml of brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with 1:1 ethyl acetate/dichloromethane to afford 1.35 g (92%) of the title product as a white solid. ¹H NMR (CDCl₃) δ 7.45-7.02 (14 H, m), 6.37-6.32 (1H, d), 4.78-20 4.72 (1H, m), 4.52-4.3 (3H, m), 3.82-3.77 (1H, m), 3.74 (3H, s), 3.03-2.87 (4H, m), 2.58-2.45 (2H, m), 2.45-2.35 (1H, m), 2.25-2.16 (1H, m).

[2-Oxo-5-(3-phenylpropionyl)-3-(3(S)-phenylpropionylamino)-2,3,4,5-

25 tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid (105b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104b; 680 mg, 1.32 mmol) was hydrolyzed by the 30 procedure used to hydrolyze 105a to afford 645 mg (98%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.56 (1H, br. s), 7.5-7.42 (1H, m), 7.35-6.95 (14H,

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m), 4.95-4.88 (1H, m), 4.64-4.55 (1H, d), 4.54-4.45 (1H, t), 4.15-4.05 (1H, d), 3.75 (1H, m), 3.05-2.75 (4H, m), 2.58-2.45 (2H, m), 2.45-2.28 (1H, m), 2.25-2.14 (1H, m).

- 5 2-Oxo-3-(S)-(2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenyl-propionyl-amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetylamino)butyric acid (106b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid and 3-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure used in the preparation of compound K (step A) to give 350 mg (85%) of a white solid. ^1H NMR (CDCl_3) δ 9.05 (1H, br. s), 7.58-7.55 (1H, d), 7.5-7.35 (1H, m), 7.35-6.95 (14 H, m), 6.75-6.72 (1H, d), 6.25 (1H, br. s), 5.25 (1H, br. s), 4.95-4.88 (1H, m), 4.8-4.72 (1H, m), 4.55-4.4 (2H, m), 3.92-3.88 (1H, d), 3.73-3.68 (1H, m), 2.95-2.8 (4H, m), 2.8-2.72 (1H, m), 2.62-2.55 (1H, m), 2.55-2.45 (2H, m), 2.4-2.32 (1H, m), 2.2-2.12 (1H, m), 1.45 (9H, s).
- 10 4-Oxo-3-(2-[2-oxo-5-(3-phenylpropionyl)-3-(3-phenyl-propionyl-amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl-amino)butyric acid tert-butyl ester semicarbazone was deprotected as described in the preparation of compound K (step C) to give 118 mg (47%) of the title compound as a white solid. ^1H NMR (CD_3OD) δ 7.48-6.95 (14 H, m), 4.65-4.15 (6H, m), 3.5-3.4 (1H, m), 2.85-2.72 (4H, m), 2.65-2.5 (1H, m), 2.5-2.34 (3H, m), 2.34-2.15 (2H, m).
- 15 [5-Benzyl-2-oxo-3-(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid
- 20 [5-Benzyl-2-oxo-3-(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid
- 25 [5-Benzyl-2-oxo-3-(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid
- 30 [5-Benzyl-2-oxo-3-(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid

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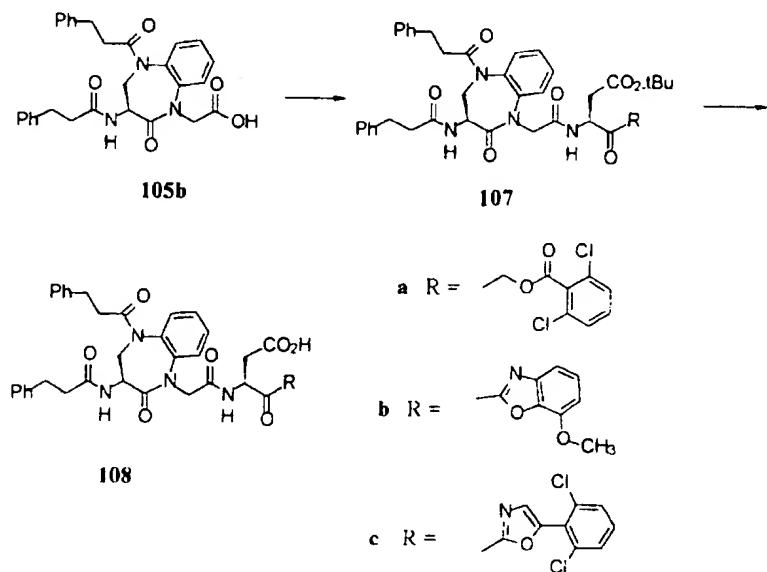
methyl ester (104c). [2-Oxo-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (**104a**; 500 mg, 1.31 mmol), calcium carbonate (155 mg, 1.58 mmol), and benzyl bromide (170 µl, 1.44 mmol) were taken into 10 ml of dimethylformamide and heated to 80 °C for 8 hours. The mixture was diluted with 150 ml of ethyl acetate and washed 4 times with 50 ml of water. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with dichloromethane/ethyl acetate (8:2) to give 460 mg (75%) of the title compound as a white solid. ^1H NMR (CDCl_3) δ 7.34-7.05 (14 H, m), 6.32-6.28 (1H, d), 4.84-4.76 (1H, d), 4.76-4.70 (1H, m), 4.43-4.37 (1H, d), 4.26-4.18 (1H, d), 4.06-4.00 (1H, d), 3.79 (3H, s), 3.45-3.37 (1H, m), 3.02-2.95 (1H, m), 2.90-2.82 (2H, m), 2.5-2.34 (2H, m).

[5-Benzyl-2-oxo-3(*S*)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid (105c) was prepared by the hydrolysis of the ester (**102c**) by the procedure reported in Example **105a** to give 450 mg (98%) of the title compound as a white solid: ^1H NMR (CD_3OD) δ 7.5-7.05 (14 H, m), 6.4 (1H, br. s), 4.85-4.55 (2H, m), 4.5-4.21 (2H, m), 4.12-3.92 (1H, d), 3.45-3.3 (1H, m), 3.1-2.8 (3H, m), 2.55-2.28 (3H, m).

3(*S*)-{2-[5-Benzyl-2-oxo-3-(3(*S*)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino}-4-oxobutyric acid (106c). {5-Benzyl-2-

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oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b[1,4]diazepin-1-yl]acetic acid and 3(S)-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure used in the preparation of compound **K** (step A) and to afford 260 mg (85%) of a white solid: ^1H NMR (CD_3OD) δ 7.35-7.0 (15 H, m), 4.94-4.88 (1H, m), 4.68-4.58 (1H, d), 4.57-4.52 (1H, m), 4.41-4.34 (1H, d), 4.3-4.23 (1H, d), 4.1-4.04 (1H, d), 3.18-3.11 (1H, m), 3.09-2.98 (1H, m), 2.78-2.72 (2H, t), -2.65-2.57 (1H, m), 2.42-2.33 (3H, m).
 3(S)-{2-[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino}-4-oxobutyric acid tert-butyl ester semicarbazone was deprotected as described in the preparation of compound K (step C) to give 168 mg (81%) of the title compound as a white solid. ^1H NMR (CD_3OD) δ 7.37-7.0 (14H, m), 4.75-4.62 (1H, m), 4.6-4.45 (2H, m), 4.4-4.21 (2H, m), 4.15-3.95 (2H, m), 3.15-3.0 (2H, m), 2.82-2.67 (2H, m), 2.65-2.52 (1H, m), 2.5-2.32 (3H, m).



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2,6-Dichlorobenzoic acid 4-tert-butoxycarbonyl-2-oxo-
3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-
phenylpropionylamino)-2,3,4,5-tetrahydro-
benzo[b][1,4]diazepin-1-yl]acetyl-amino}butyl ester

5 (107a). The resulting semicarbazone was prepared by
the coupling of compound 105b and t-butyl 3-
(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-
oxy)pentanoate (WO 93 16710) as described in compound
56a to give 256 mg (58%) of the title compound as a
10 white solid. ^1H NMR (CDCl_3) δ 7.45-7.04 (17H, m), 6.45-
6.34 (2H, m), 5.28-5.21 (1H, m), 5.1-5.0 (1H, m), 4.95-
4.90 (1H, m), 4.75-4.70 (1H, m), 4.55-4.44 (1H, m),
4.32-4.22 (1H, dd), 3.99-3.85 (1H, dd), 3.85-3.76 (1H,
m), 3.06-2.83 (5H, m), 2.83-2.74 (1H, m), 2.6-2.44 (2H,
m), 2.43-2.33 (1H, m), 2.24-2.15 (1H, m), 1.45 (9H, s).

2,6-Dichlorobenzoic acid 4-carboxy-2-oxo-3(S)-{2-[2-
oxo-5-(3-phenylpropionyl)-3(S)-{(3-
phenylpropionylamino)-2,3,4,5-
tetrahydrobenzo[b][1,4]diazepin-1-yl]acetylamino}butyl

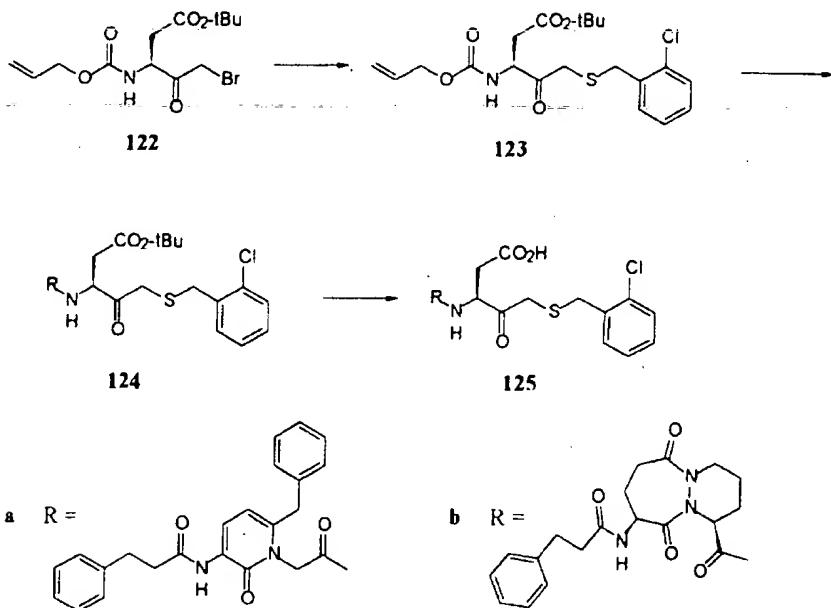
20 ester (108a) was prepared from 107a by the method
described for compound 57a which afforded 156 mg (68%)
of the title compound as a white solid. ^1H NMR (CD_3OD)
 δ 7.5-6.9 (17H, m), 5.16-5.02 (1H, dd), 4.88-4.71 (2H,
m), 4.62-4.44 (2H, m), 4.42-4.28 (2H, m), 4.27-4.18
25 (1H, m), 3.47-3.41 (1H, m), 2.90-2.60 (5H, m), 2.46-2.4
(2H, m), 2.39-2.18 (2H, m).

4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(S)-{2-[2-oxo-5-(3-
phenylpropionyl)-3(S)-{(3-phenylpropionylamino)-2,3,4,5-
tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino}

30 butyric acid (108b) was prepared by the method

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described for compound **69a** to give the title compound (50%) as a white solid. ^1H NMR (CD_3OD) δ 7.41-6.88 (17H, m), 5.6-5.55 (0.5H, t), 5.48-5.43 (0.5H, t), 4.64-4.45 (2H, m), 4.45-4.30 (1H, m), 3.93 (1.5H, s), 5 3.90 (1.5H, s), 3.47-3.34 (1H, m), 3.10-2.85 (2H, m), 2.84-2.63 (5H, m), 2.6-2.4 (2H, m), 2.3-2.1 (2H, m).



t-Butyl (3S) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxo-pentanoate (123).

Potassium fluoride (273mg, 4.70mmol) and then 2-
10 chlorophenylmethyl thiol (373mg, 2.35mmol) were added
to a stirred solution of (3S) t-butyl N-
(allyloxycarbonyl)-3-amino-5-bromo-4-oxo-pentanoate
(**122**; 749mg, 2.14mmol; WO 93 16710) in
dimethylformamide (20ml). The mixture was stirred for
15 3.5h, quenched with water (50ml) and extracted with
ethyl acetate (2 x 50ml). The combined organic
extracts were washed with water (4 x 50ml) then brine

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(50ml). They were dried ($MgSO_4$) and concentrated to afford an oil which was purified by flash chromatography (10-35% ethyl acetate/hexane) to afford 832 mg (91%) of a colourless solid: mp. 45-6 °C; $[\alpha]_D^{20}$ -19.0° (c 1.0, CH_2Cl_2); IR (film) 3340, 2980, 2935, 1725, 1712, 1511, 1503, 1474, 1446, 1421, 1393, 1368, 1281, 1244, 1157, 1052, 1040, 995, 764, 739; 1H NMR ($CDCl_3$) δ 7.36 (2H, m), 7.21 (2H, m), 5.91 (2H, m), 5.27 (2H, m), 4.76 (1H, m), 4.59 (2H, d), 3.78 (2H, s), 3.36 (2H, m), 2.91 (1H, dd), 2.74 (1H, dd), 1.43 (9H, s). Anal. Calcd for $C_{20}H_{26}ClNO_5S$: C, 56.13; H, 6.12; N, 3.27; S, 7.49. Found: C, 56.08; H, 6.11; N, 3.26; S, 7.54. MS (C.I.) 430/28 ($M^+ + 1$, 3%), 374/2 (100).

t-Butyl (3*S*) 3(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetylamino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a). 6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-pyridyl acetic acid (52b; 300mg, 0.76mmol) in THF (7ml) was stirred with 1-hydroxybenzotriazole (205mg, 1.52mmol) and 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride). After 3 min, water (12 drops) was added and the mixture stirred 10min then treated with t-butyl (3*S*) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (123) (325mg, 0.76mmol), bis (triphenylphosphine) palladium II chloride (20mg) and tributyltin hydride (0.6ml, 2.28mmol). The mixture was stirred for 5h at room temperature, poured into ethyl acetate and washed with aqueous 1M HCl (x2), aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and concentrated. The residue was triturated with pentane and the supernatant discarded. Chromatography (silica gel, 50% ethyl acetate/hexane)

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afforded a colourless foam (439mg, 81%): $[\alpha]_D^{25} -18.3^\circ$ (c 0.5, CH_2Cl_2); IR (KBr) 3356, 3311, 1722, 1689, 1646, 1599, 1567, 1513, 1367, 1154; ^1H NMR (CDCl_3) δ 8.39 (1H, d), 8.23 (1H, s), 7.24 (14H, m), 6.16 (1H, d), 4.95 (1H, m), 4.63 (2H, m), 4.02 (2H, s), 3.74 (2H, s), 3.27 (2H, s), 2.85 (6H, m), 1.40 (9H, s). Anal. Calcd for $\text{C}_{39}\text{H}_{42}\text{ClN}_3\text{O}_6\text{S}$: C, 65.39; H, 5.91; N, 5.87. Found: C, 65.51; H, 5.99; N, 5.77.

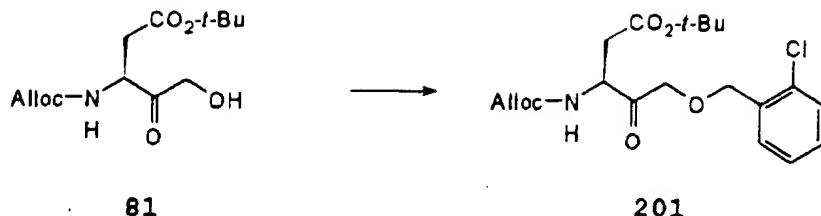
- t-Butyl [3*S*(1*S*,9*S*)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124b) was prepared by a similar method as 124a from the thioether 123 and 3*S*(1*S*,9*S*)-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a) to afford 452mg (50%) of colourless foam: mp 55-7 °C; $[\alpha]_D^{22} -94.0^\circ$ (c 0.12, CH_2Cl_2); IR (KBr) 3288, 2934, 1741, 1722, 1686, 1666, 1644, 1523, 1433, 1260, 1225, 1146, 757; ^1H NMR (CDCl_3) δ 7.35 (3H, m), 7.20 (7H, m), 6.46 (1H, d), 5.21 (1H, m), 4.97 (2H, m), 4.56 (1H, m), 3.75 (2H, s), 3.25 (3H, m), 2.93 (5H, m), 2.71 (1H, dd), 2.55 (2H, m), 2.30 (1H, m), 1.92 (3H, m), 1.66 (2H, m), 1.42 (9H, s). Anal. Calcd for $\text{C}_{35}\text{H}_{43}\text{ClN}_4\text{O}_7\text{S}$: 0.25 H_2O : C, 59.73; H, 6.23; Cl, 5.04; N, 7.96; S, 4.56. Found: C, 59.73; H, 6.19; Cl, 5.10; N, 7.79; S, 4.58. MS (-FAB) 697 (M-1, 100).
- (3*S*) 3(2(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetylamino-5-(2-chlorophenylmethylthio)-4-oxopentanoic acid (125a).

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t-Butyl-3-(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (**124a**) (400mg, 0.56mmol) in dichloromethane (3ml) at 0 °C was treated
5 with trifluoroacetic acid (3ml) and stirred at 0 °C for 1h and room temperature for 0.5h. The solution was concentrated then redissolved in dichloromethane and reconcentrated. This procedure was repeated three times. The residue was stirred in ether for 1hr and
10 filtered to yield a colourless solid (364mg, 99%): mp. 165-7 °C; $[\alpha]_D^{22} -27.7^\circ$ (c 0.2, CH₂Cl₂); IR (KBr) 3289, 1712, 1682, 1657, 1645, 1593, 1562, 1527, 1497, 1416, 1203, 1182; ¹H NMR (CDCl₃) δ 8.47 (1H, d), 8.21 (1H, s), 7.70 (1H, d), 7.22 (14H, m), 6.24 (1H, d), 5.03 (1H, m), 4.65 (2H, m), 4.06 (2H, s), 3.69 (2H, m), 3.23 (2H, m), 2.88 (6H, m).

[3S(1S,9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-
9-(3-phenylpropionyl-amino)-6H-
pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-
20 chlorophenyl-methylthio)-4-oxopentanoic acid (**125b**),
was prepared by a similar method as **125a** from the t-
butyl ester **124b** to afford 362mg (93%) of colourless
powder: mp 76-80 °C; $[\alpha]_D^{21} -134^\circ$ (c 0.10, MeOH); IR
(KBr) 3309, 2935, 1725, 1658, 1528, 1445, 1417, 1277,
25 1219, 1175; ¹H NMR (D₆-DMSO) δ 8.80 (1H, d), 8.19 (1H, d), 7.31 (9H, m), 5.09 (1H, m), 4.74 (1H, m), 4.63 (1H, m), 4.35 (1H, m), 3.76 (2H, m), 3.28 (3H, m), 2.80 (5H, m), 2.52 (4H, m), 2.16 (2H, m), 1.90 (3H, m). Anal.
Calcd for C₃₁H₃₅Cl₂N₄O₇S. 0.25H₂O: C, 57.49; H, 5.53;
30 N, 8.65; S, 4.95. Found: C, 57.35; H, 5.43; N, 8.45;
S, 4.88.. MS (-FAB) 641 (M-1, 100%).

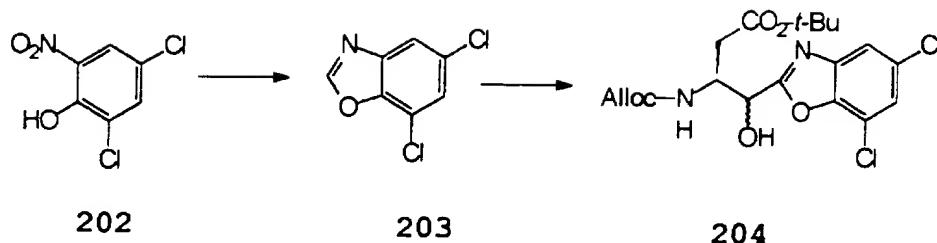
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2-Chlorophenylmethyliodide. A mixture of 2-chlorophenylmethylbromide (4g, 19.47mmol) and NaI (14g, 97.33mmol) in acetone (40ml) was stirred under reflux for 1 hour. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was triturated with hexane and filtered. The solution was concentrated *in vacuo*, and the resulting oil purified by flash chromatography (silica, hexane) to afford the title compound (4.67g, 63%) as an oil: ^1H NMR (CDCl_3) δ 7.34 (4H, m), 4.54 (2H, s).

(3S) t-Butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethyloxy)-4-oxopentanoate (201). (3S) t-Butyl N-(allyloxycarbonyl)-3-amino-5-hydroxy-4-oxopentanoate (81, Chapman, et al., *Bioorg. & Med. Chem. Lett.*, 2, pp. 613-618 (1992) 0.144g, 0.5mmol) and 2-chlorophenylmethyliodide (0.569g, 1.5mmol) in CH_2Cl_2 (4ml) were stirred vigorously with silver oxide (0.231g, 1mmol) and heated at 38 °C for 40 hours. The reaction mixture was cooled, filtered and the filtrate evaporated. The residue was purified by flash chromatography (silica, 0-20% ethylacetate in hexane) to afford the product as a colourless oil (0.138g, 67%): $[\alpha]_D^{24} +3.9^\circ$ (c 1.3, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.37 (4H, m), 5.88 (2H, m), 5.26 (2H, m), 4.69 (2H, s), 4.57 (3H, m), 4.50 (1H, d), 4.35 (1H, d), 3.03 (1H, dd), 2.76 (1H, dd), 1.42 (9H, s).

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5,7-Dichlorobenzoxazole (203). A solution of 2,4-dichloro-6-nitrophenol (**202**, 40g containing 20% moisture) in EtOAc (500ml) was dried using MgSO₄, filtered and the filter cake washed with a little

- 5 EtOAc. Platinum on carbon (5% sulphided - 2g) was added and the mixture hydrogenated until uptake of H₂ ceased. Triethyl orthoformate (160ml) and p-toluene sulphonic acid (160mg) were added and the mixture refluxed for 4h. After cooling and removal of spent
- 10 catalyst by filtration the solution was washed with sat. NaHCO₃ solution, water and brine, dried with MgSO₄ and evaporated to dryness. Trituration with hexane gave a solid which was collected by filtration, washed with hexane and dried to give the title compound
- 15 (25.5g, 88%) as a crystalline solid: mp 98-99 °C; IR (KBr) 3119, 1610, 1590, 1510, 1452, 1393, 1296, 1067, 850; ¹H NMR (CDCl₃) δ 8.16 (1H, s), 7.69 (1H, d, J = 1.9), 7.42 (1H, d, J = 1.9); Anal. Calcd for C₇H₃Cl₂NC: C, 44.72; H, 1.61; N, 7.45; Cl, 37.70. Found: C, 44.84; H, 1.69; N, 7.31; Cl, 37.71.

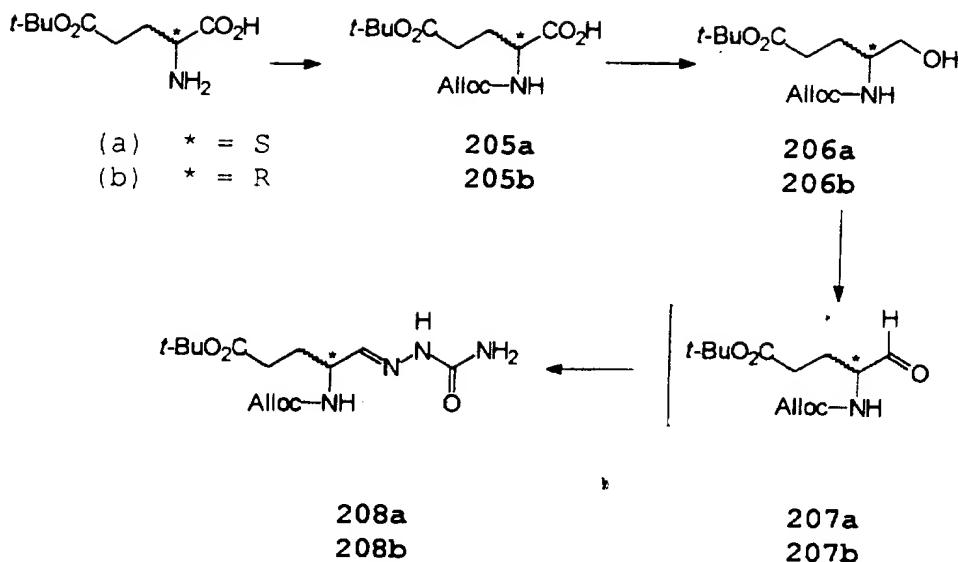
(3S,4RS) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204).

- Magnesium bromide was prepared by reaction of Mg (7.45g, 0.30mole) in THF (516ml) with I₂ (50mg) and
- 25 1,2-dibromoethane (26.3ml, 57.3g, 0.30mole) at reflux for 2h and then cooling to -40 °C. To the above was

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added rapidly via cannula a solution of 2-lithio-5,7-dichlorobenzoxazole at 70 °C (prepared from 5,7-dichlorobenzoxazole (**203**, 28.9g, 0.154mole) and butyl lithium (100ml 1.52M in hexane) in THF (150ml) at 5 70 °C). The mixture was stirred at -40 °C for 1h and then cooled to -70 °C before adding a solution of (3S)-t-butyl N-(allyloxycarbonyl)-3-amino-4-oxo-butanoate (Chapman, et al., Bioorg. & Med. Chem. Lett., 2, pp. 613-618 (1992)) (20.3g, 0.078mole) in THF (160ml) at 10 less than -60 °C. The reaction was allowed to warm to ambient temperature and was stirred for 16h before quenching with ammonium chloride solution and extracting with 1:1 hexane:ethylacetate 600ml. The organic solution was washed with water and brine, dried 15 with MgSO₄ and evaporated to a syrup (52.9g). Flash chromatography (SiO₂ 250g -11 aliquots of 1:1 hexane:CH₂Cl₂ ×2, CH₂Cl₂, 5% EtOAc in CH₂Cl₂, 10% EtOAc in CH₂Cl₂, 20% EtOAc in CH₂Cl₂) gave impure product 24.6g which on further chromatography (SiO₂ 1:1 hexane:ether) 20 give the title compound as a golden-brown glass (22.7g, 64%); IR (film) 3343, 2980, 1723, 1712, 1520, 1456, 1398, 1369, 1254, 1158, 993; ¹H NMR (CDCl₃) δ 7.60 (1H, m), 7.37 (1H, m), 5.72 (1H, m), 5.64 (0.5H, d), 5.10 (2.5H, m), 4.7-4.3 (4H, m), 2.9-2.6 (2H, m), 1.46 and 25 1.42 (9H combined, 2 x s). MS ES⁺ Da/e 445 (M + 1)⁺ Cl 35 62%, 447 (M + 1)⁺ Cl 37 40%, 389 100%.

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(2S)-N-Allyloxycarbonyl-5-(1,1-dimethylethyl)glutamate (205a).

To a mixture of THF (200ml) and water (100ml) containing NaHCO_3 (16.6g, 0.2mol) was added glutaric acid *t*-butyl ester (10g, 49.2mmol) and then dropwise over 20 minutes allyl chloroformate (6.8ml, 64mmol).

The mixture was stirred for 2 hours, extracted with EtOAc, washed with a sat. hydrogenocarbonate solution, water and a sat. salt solution, dried and evaporated to an oil **205a** (9.5g, 67.2%); $[\alpha]_D^{20} -6^\circ$ (c 1.5, MeOH)

1^H NMR (D_6 -DMSO) δ 6.10 (1H, d), 5.96-5.88 (1H, m), 5.31-5.12 (2H, m), 4.45 (2H, m), 3.90-3.84 (1H, t), 2.18 (2H, m), 1.85-1.76 (2H, m), 1.36 (9H, s).

(2R)-N-Allyloxycarbonyl-5-(1,1-dimethylethyl)glutamate (205b), was prepared by an analogous method to **205a** to afford a colourless oil (6.27g, 88%); $[\alpha]_D^{20} +16^\circ$ (c 0.095, MeOH); IR (KBr) 3678, 3332, 3088, 2980, 2937, 1724, 1530, 1453, 1393, 1370, 1331, 1255, 1155, 1056, 995, 935, 845, 778, 757, 636, 583; ¹H NMR ($CDCl_3$) δ

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9.24 (1H, broad s), 5.94-5.79 (1H, m), 5.58 (1H, d),
5.33-5.17 (2H, m), 4.55 (2H, d), 4.38-4.31 (1H, m),
2.41-1.95 (4H, m), 1.42 (9H, s); Anal. Calcd for
 $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C,
5 54.4; H, 7.5; N, 4.8.

(4S) t-Butyl N-allyloxycarbonyl-4-amino-5-hydroxypentanoate (206a). To a solution of 205a (3.6g, 12.5mmol) in THF (100ml) at 0 °C was added N-methylmorpholine (1.5ml, 13mmol) followed by isobutyl 10 chloroformate, (1.1ml, 13mmol). After 15 minutes, this mixture was added to a suspension of NaBH₄ (0.95g, 25mmol) in THF (100ml) and MeOH (25ml) at -78 °C. After 2 hours at -70 °C, the mixture was quenched with acetic acid, diluted with EtOAc, washed with a sat. 15 hydrogenocarbonate solution 3 times, water and a sat. solution of salt, dried and evaporated. Flash chromatography (2% MeOH in CH₂Cl₂) afforded 206a as a colourless oil (2.4g, 70%): $[\alpha]_D^{20}$ -10 ° (c 3.88, CH₂Cl₂); ¹H NMR (CDCl₃) δ 5.84 (1H, m), 5.34-5.17 (3H, 20 m), 4.56-4.53 (2H, m), 3.68-3.59 (2H, m), 2.98 (1H, m), 2.40-2.30 (2H, t), 1.84-1.78 (2H, m), 1.43 (9H, s); Anal. Calcd for C₁₃H₂₃NO₅: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.1; H, 8.6; N, 6.0

(4R) t-Butyl N-allyloxycarbonyl-4-amino-5-hydroxypentanoate (206b), was prepared by an analogous 25 method to 206a which afforded the title compound as a light yellow oil (3.42g, 57%): $[\alpha]_D^{20}$ +14 (c 0.166, MeOH); IR (KBr) 3341, 3083, 2976, 2936, 2860, 1724, 1533, 1454, 1419, 1369, 1332, 1251, 1156, 1062, 997, 30 933, 846, 777, 647; ¹H NMR (CDCl₃) δ 5.98-5.81 (1H, m), 5.35-5.10 (3H, m), 4.55 (2H, d), 3.70-3.56 (3H, m),

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2.50-2.47 (1H, broad s), 2.37-2.30 (2H, m), 1.89-1.74 (2H, m), 1.44 (9H, s); Anal. Calcd for C₁₃H₂₃NO₅: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.9; H, 8.6; N, 5.6

5 **(4S) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate (207a).** To a solution of DMSO (1.51g, 19.3mmol) in CH₂Cl₂ (25ml) at -70 °C was added oxalyl chloride (1.34g, 19.3mmol). After 10 minutes at -70 °C, a solution of (206a) (2.4g, 8.8mmol) in CH₂Cl₂ (10ml) was
10 added dropwise and the mixture stirred for 15 minutes at -70 °C. Diisopropylethylamine (3.4g, 26.3mmol) was added and the mixture stirred at -25 °C for 15 minutes then diluting with EtOAc (50ml) washed with a solution of sodium hydrogen sulfate 2M, concentrated to give an
15 oil which was used immediately without purification:
¹H NMR (CDCl₃) δ 9.5 (1H, s), 6.0-5.5 (2H, m), 5.5-5.1 (2H, m), 4.5 (2H, m), 4.2 (1H, m), 2.4-2.10 (2H, m), 2.05 (2H, m), 1.36 (9H, s).

20 **(4R) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate (207b),** was prepared by an analogous method to 207a which afforded an oil (2.95g, 96%) which was used without further purification in the next step: [α]_D²⁰ +21 ° (c 0.942, MeOH); ¹H NMR (CDCl₃) δ 9.58 (1H, s), 6.05-5.80 (1H, m), 5.57 (1H, broad s), 5.35-5.18 (2H, m), 4.56 (2H, d), 4.34-4.24 (1H, m), 2.38-2.16 (3H, m), 1.96-1.73 (1H, m), 1.43 (9H, s).

25 **(4S) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate semicarbazone (208a).** To a solution of 207a (2.39g, 8.8mmol), in MeOH (20ml) was added sodium acetate (0.72g, 8.8mmol) and semicarbazide (0.98g, 8.8mmol)

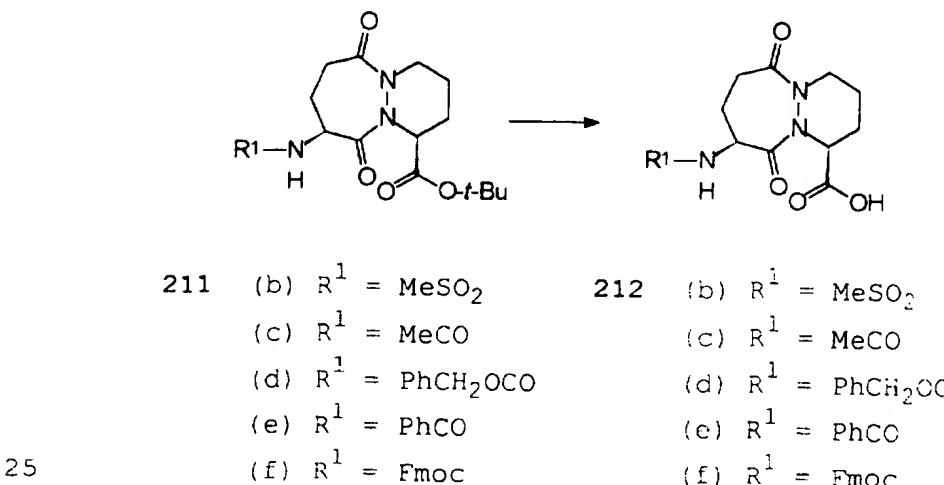
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stirred overnight, concentrated and diluted with CH_2Cl_2 (100ml), washed with water, dried and concentrated.

Flash chromatography (2% MeOH in CH_2Cl_2) afforded **208a** (2.10g, 73%) as an oil: $[\alpha]_D^{20} -21$ (*c* 2.55 °, CH_2Cl_2);

5 ^1H NMR (CDCl_3) δ 9.98 (1H, s), 7.27 (1H, d), 5.8 (1H, m), 5.5 (1H, d), 5.35-5.19 (2H, m), 4.58 (2H, m), 4.14 (1H, m), 2.37 (2H, t), 2.09 (1H, m), 2.0-1.75 (2H, m);
Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{N}_4\text{O}_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 50.2; H, 7.3; N, 16.1

10 (*4R*) *t*-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate semicarbazone (**208b**), was prepared by an analogous method to **208a** which afforded a glassy oil (2.37g, 66%): $[\alpha]_D^{20} +30$ (*c* 0.26, CHCl_3); IR (KBr) 3476, 3360, 2979, 2923, 1700, 1586, 1527, 1427, 1394, 1369, 1338, 1253, 1156, 1060, 997, 929, 846, 775; ^1H NMR (CDCl_3) δ 9.87 (1H, s), 7.09 (1H, d), 6.05-5.75 (3H, m), 5.58 (1H, d), 5.32-5.16 (2H, m), 4.54 (2H, d), 4.35 (1H, m), 2.32-2.26 (2H, m), 2.15-1.55 (2H, m), 1.41 (9H, s);
Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{N}_4\text{O}_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 51.0; H, 7.5; N, 16.7.



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- (1*S*,9*S*) t-Butyl 6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (211b). A solution of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 831mg, 2.79mmol) and diisopropylethylamine (1.22ml, 6.99mmol, 2.5 equiv) in CH₂Cl₂ (10ml) under dry nitrogen was treated with methanesulphonyl chloride (237μl, 3.07mmol 1.1 equiv).
- The mixture was stirred for 1h, diluted with EtOAc (75ml) and washed with saturated NaHCO₃ (50ml) and saturated aqueous sodium chloride (30ml), dried (MgSO₄) and concentrated. Flash chromatography (10-35% EtOAc in CH₂Cl₂) afforded 211b (806mg, 77%) as a colourless solid: mp 68-70 °C; [α]_D²³ -109 (c 1.09, CH₂Cl₂); IR (KBr) 3270, 2980, 2939, 1735, 1677, 1458, 1447, 1418, 1396, 1370, 1328, 1272, 1252, 1232, 1222, 1156, 1131, 991; ¹H NMR (CDCl₃) δ 6.15 (1H, d), 5.31 (1H, m), 4.65-4.11 (2H, m), 3.47 (1H, m) 2.99 (3H, s), 2.89 (1H, m), 2.72-2.51 (2H, m), 2.34 (1H, m), 2.26 (1H, m), 2.05-1.62 (4H, m), 1.47 (9H, s); Anal. Calcd for C₁₅H₂₃N₃O₆S: C, 47.97; H, 6.71; N, 11.19; S, 8.54. Found: C, 48.28; H, 6.68; N, 10.86; S, 8.28. MS (+ FAB) 376 (M⁺ + 1, 66%), 320 (100).
- (1*S*,9*S*) t-Butyl 9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a]-[1,2]diazepine-1-carboxylate (211c). Acetic anhydride (307mg, 3.01mmol) was added to a stirred mixture of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 813.7mg, 2.74mmol), diisopropylethylamine (884mg, 6.84mmol) and CH₂Cl₂

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(20ml). The mixture was kept for 1h then diluted with EtOAc, washed with NaHCO₃ solution then brine, dried (MgSO₄) and concentrated to yield a colourless oil. The product was purified by flash chromatography (0.5-5 8% MeOH/CH₂Cl₂) to afford **211c** (804mg, 71%) of colourless powder: mp 162-3 °C; [α]_D²³ -109 (c 1.03, CH₂Cl₂); IR(KBr) 3358, 2974, 1733, 1693, 1668, 1528, 1462, 1431, 1406, 1371, 1278, 1271, 1250, 1233, 1217, 1154, 1124; δ ¹H NMR (CDCl₃) δ 6.32 (1H, d), 5.29-5.25 (1H, m), 4.98-4.85 (1H, m), 4.68-4.58 (1H, m), 3.55-3.39 (1H, m), 2.91-2.66 (2H, m), 2.39-2.18 (2H, m), 2.03 (3H, s), 1.88-1.64 (4H, m), 1.47 (9H, s); Anal. Calcd for C₁₆H₂₅N₃O₅: C, 56.62; H, 7.43; N, 12.38. Found: C, 56.62; H, 7.43; N, 12.36; MS (+ FAB) 340 (M⁺ + 1, 40%), 284 (100).

(1S,9S) t-Butyl 9-(benzyloxycarbonylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (**211d**). Benzyl chloroformate (1.07g) was added dropwise to a stirred ice cold 20 mixture of the (1S,9S) t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 1.55g, 5.21mmol), NaHCO₃ (0.66g, 7.82mmol), dioxan (32ml) and water (8ml). The mixture was kept at 5 °C for 15min 25 then for 2h at room temperature. The mixture was diluted with EtOAc (50ml), washed twice with sat. NaHCO₃ solution, dried (MgSO₄) and concentrated. The oily residue was purified by flash chromatography to afford **211d** (1.98g, 88%) of a colourless oil: [α]_D²⁴ - 30 56.4 (c 1.0, CH₂Cl₂); IR(thin film) 3325, 2979, 2946, 1728, 1677, 1528, 1456, 1422, 1370, 1340, 1272, 1245, 1156, 1122, 1056, 916, 734, 699; ¹H NMR (CDCl₃) δ 7.29

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(5H, m), 5.81-5.72 (1H, m), 5.26-5.20 (1H, m), 5.05
(2H, s), 4.69-4.51 (2H, m), 3.48-3.36 (1H, m), 2.81-
2.51 (2H, m), 2.34-2.19 (2H, m), 1.90-1.54 (4H, m),
1.41 (9H, s); Anal. Calcd for $C_{22}H_{29}N_3O_6 \cdot H_2O$: C, 58.79;
5 H, 6.92; N, 9.35. Found: C, 59.10; H, 6.57; N, 9.25;
MS (ES +) 454 ($M^+ + Na$, 87%), 432 ($M^+ + 1$, 100).

(1S,9S) t-Butyl 9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylate (211e). A solution of benzoyl
10 chloride (1.61g, 11.47mmol) in CH_2Cl_2 (15ml) was added dropwise to a stirred ice cold mixture of (1S,9S) t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate
(GB 2,128,984; 3.1g, 10.43mmol), dry CH_2Cl_2 (20ml) and
15 diisopropylethylamine (4.54ml, 26.06mmol). The mixture was kept cold for 1h then left at room temperature for 0.5h. The mixture was diluted with CH_2Cl_2 , washed twice with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-5%
20 methanol in CH_2Cl_2) to afford **211e** (4.0g, 96%) of a colourless glass: mp 74-76 °C; $[\alpha]_D^{30} -75.0$ ° (c 0.12, CH_2Cl_2). IR (KBr) 3350, 2979, 2938, 1736, 1677, 1662, 1536, 1422, 1276, 1250, 1155; 1H NMR ($CDCl_3$) δ 8.72
(2H, m), 7.53-7.40 (3H, m), 7.07 (1H, d, $J = 7.2$), 5.30
25 (1H, dd, $J = 3.0, 5.8$), 5.12 (1H, m), 4.66 (1H, m), 3.51 (1H, m), 2.90 (2H, m), 2.38 (1H, dd, $J = 13.2, 6.8$), 2.25 (1H, m), 1.9 (2H, m), 1.70 (1H, m). Anal. Calcd
for $C_{21}H_{27}N_3O_5 \cdot 0.5H_2O$: C, 61.45; H, 6.88; N, 10.24.
Found C, 61.69; H, 6.71; N, 10.18.

30 **(1S,9S) t-Butyl 6,10-dioxo-9-(fluoren-9-ylmethoxy-carbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-**

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pyridazino[1,2-a][1,2]-diazepine-1-carboxylate (211f),

was prepared in a similar manner to 211e, except 9-fluorenylmethylchloroformate was used instead of benzoylchloride to give a white glassy solid 211f

- 5 (2.14g, 89%): mp 190-192 °C; $[\alpha]_D^{25} -81.5^\circ$ (c 0.1, CH₂Cl₂). IR (KBr) 3335, 2977, 1731, 1678, 1450, 1421, 1246, 1156, 742; ¹H NMR (CDCl₃) δ 7.60 (2H, m), 7.57 (2H, m), 7.50-7.26 (4H, m), 5.60 (1H, d, J = 7.8), 5.28 (1H, m), 4.67 (2H, m), 4.38 (2H, m), 4.23 (1H, m), 10 3.59-3.41 (1H, m), 2.92-2.65 (2H, m), 2.41-2.21 (2H, m), 1.95-1.58 (4H, m), 1.47 (9H, s). MS(ES⁻, m/z) 520 (M⁺ + 1, 97%), 179 (100%).

(1S,9S) 6,10-Dioxo-9-methysulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

- 15 **[1,2-a][1,2]diazepine-1-carboxylic acid (212b),** was synthesized by the same method as compound 212e (635mg, 85%) as a colourless powder: mp 209-12 °C; $[\alpha]_D^{24} -132$ (c 0.12, MeOH); IR (KBr) 3308, 2940, 1717, 1707, 1699, 1619, 1469, 1456, 1442, 1417, 1391, 1348, 1339, 1330, 20 1310, 1271, 1247, 1222, 1175, 1152, 1133, 993, 976; ¹H NMR (CD₃OD) δ 5.35 (1H, m), 4.58-4.48 (1H, m), 4.46-4.36 (1H, m), 3.60-3.42 (1H, m), 3.01-2.87 (1H, m), 2.95 (3H, s), 2.55-2.39 (1H, m), 2.32-2.20 (2H, m), 2.09-1.89 (2H, m), 1.78-1.62 (2H, m); Anal. Calcd for 25 C₁₁H₁₇N₃O₆S: C, 41.37; H, 5.37; N, 13.16; S, 10.04. Found: C, 41.59; H, 5.32; N, 12.75; S, 9.76; MS(ES⁻): Accurate Mass calculated for C₁₁H₁₈N₃O₆S (MH⁺): 320.0916. Found: 320.0943.

(1S,9S) 9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-

- 30 **octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (212c),** was prepared from 211e the same

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method as compound **212e** as a white glassy solid (595mg, 77%): mp >250 °C; $[\alpha]_D^{24}$ -153 (c 0.10, MeOH); IR (KBr) 3280, 2942, 1742, 1697, 1675, 1650, 1616, 1548, 1470, 1443, 1281, 1249, 1202, 1187, 1171; ^1H NMR (CD_3OD) δ

5 5.35-5.31 (1H, m), 4.81-4.71 (1H, m), 4.61-4.46 (1H, m), 3.59-3.44 (2H, m), 3.11-2.94 (1H, m), 2.58-2.39 (1H, m), 2.36-2.19 (2H, m), 2.11-1.83 (3H, m), 1.99 (3H, s), 1.78-1.56 (2H, m); Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_5$: C, 50.88; H, 6.05; N, 14.83. Found: C, 50.82; H, 6.02; N, 14.58; MS (ES -) 282 (M-1, 100%); Accurate Mass calculated for $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}_5$ (MH^+): 284.1246. Found: 284.1258.

(*1S,9S*) 9-Benzylloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-

15 [1,2-a][1,2]diazepine-1-carboxylic acid (**212d**), was prepared from **211d** by the same method as compound **212e** as colourless crystals (170mg, 97%): mp 60-100 °C; $[\alpha]_D^{22}$ -103 (c 0.10, MeOH); IR (KBr) 3341, 2947, 1728, 1675, 1531, 1456, 1422, 1339, 1272, 1248, 1221, 1174, 20 1122, 1056, 982, 699; ^1H NMR (CDCl_3) δ 7.35 (5H, s), 5.65 (1H, d), 5.48-5.40 (1H, m), 5.10 (2H, s), 4.76-4.57 (2H, m), 3.49-3.30 (2H, m), 2.92-2.59 (2H, m), 2.40-2.27 (2H, m), 1.97-1.67 (4H, m); MS (ES -) 374 (M - 1, 100%). Accurate mass calculated for $\text{C}_{18}\text{H}_{22}\text{N}_3\text{C}_6$ 25 (MH^+): 376.1509. Found: 376.1483. Accurate mass calculated for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_6\text{Na}$ (MNa^+): 398.1328. Found: 398.1315.

(*1S,9S*) 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-a][1,2]-diazepine-1-

30 carboxylic acid (**212e**). TFA (20ml) was added to an ice cold stirred solution of the t-butyl ester **211e** (4.15g,

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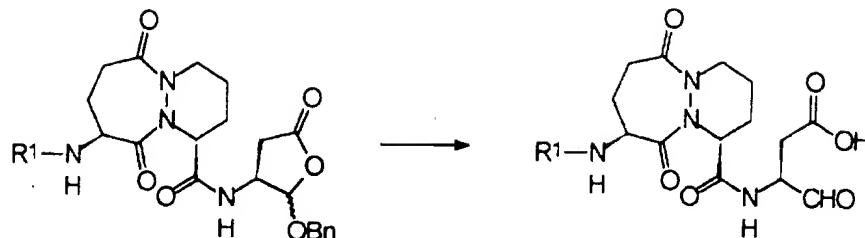
10.34mmol) in dry CH_2Cl_2 (20ml). The mixture was kept cold for 1.5h then left for 2.5h at rt, concentrated. TFA was removed by repeated concentrations of CH_2Cl_2 \ether and ether solutions of the residue.

- 5 Finally trituration of the residue with ether afforded **212e** 3.05g (85%) of a white glassy solid: mp 118-
126 °C; $[\alpha]_D^{24} -70.5^\circ$ (c 0.1, CH_2Cl_2). IR (KBr) 3361,
2943, 1737, 1659, 1537, 1426, 1220, 1174; ^1H NMR
(CDCl_3) δ 7.80 (2H, m), 7.54-7.33 (4H, m), 8.83 (brs),
10 5.44 (1H, m), 5.26-5.13 (1H, m), 4.66 (1H, m), 3.59-
3.41 (1H, m), 2.97, 2.76 (2H, 2m), 2.36 (2H, m), 1.98
(2H, m), 1.75 (2H, m). MS(ES⁻, m/z) 344 (M - 1, 100%).

(1S,9S) 6,10-Dioxo-9-(fluoren-9-
ylmethoxy carbonylamino)-1,2,3,4,7,8,9,10-octahydro-

- 15 **6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid**
(212f), was prepared from **211f** in 96% yield by the same
method as for **212e**: mp 120-126 °C; $[\alpha]_D^{25} -72.5^\circ$
(c 0.1, CH_2Cl_2). IR (KBr) 3406, 2950, 1725, 1670,
1526, 1449, 1421, 1272, 1248, 1223, 1175, 761, 741;
20 ^1H NMR (CDCl_3) δ 7.76 (2H, m), 7.62-7.26 (4H, m), 6.07,
5.76 (2H, brs, d, d, $J = 2.9$), 5.46, 5.36 (1H, 2m),
4.79-4.54 (2H, m), 4.77 (2H, m), 4.21 (1H, m), 3.41
(1H, m), 2.89 (1H, m), 2.69 (1H, m), 2.35 (2H, m),
1.98, 1.73 (4H, 2m). MS(ES⁻, m/z) 462 (M⁺ - 1, 50%),
25 240 (100%).

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(213) (c) $R^1 = MeCO$
(e) $R^1 = PhCO$

(214) (c) $R^1 = MeCO$
(e) $R^1 = PhCO$

[2RS,3S(1S,9S)] N-(2-Benzyl-oxo-5-oxotetrahydrofuran-3-yl)-9-(acetylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-

5 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213c), was synthesized from 212c by the same method as compound 213e to afford a mixture of diastereomers (193mg, 36%) as colourless crystals: IR (KBr) 3272, 1799, 1701, 1682, 1650, 1555, 1424, 1412, 10 1278, 1258, 1221, 1122, 937; 1H NMR ($CDCl_3$) δ 7.41-7.28 (5H, m), 6.52 (0.5H, d), 6.38 (0.5H, d), 6.22 (0.5H, d), 5.57 (0.5H, d), 5.36 (0.5H, s) 5.10-5.05 (1H, m), 5.00-4.45 (5.5H, m), 3.19-2.84 (3H, m), 2.72-2.56 (1H, m), 2.51-2.25 (2H, m), 2.02 (3H, s), 1.98-1.70 (3H, m), 15 1.66-1.56 (3H, m); Anal. Calcd for $C_{23}H_{28}N_4O_7$: C, 58.47; H, 5.97; N, 11.86. Found: C, 58.37; H, 6.09; N, 11.47. MS (ES-) 471 (M-1, 100%). Accurate mass calculated for $C_{23}H_{29}N_4O_7$ (MH^+): 473.2036. Found: 473.2012. Accurate mass calculated for $C_{23}H_{28}N_4O_7Na$ 20 (Mn^{+}): 495.1856. Found: 495.1853.

[1S,9S(2RS,3S)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-benzyl-oxo-5-

25 oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamide (213e). Tributyltin hydride (2.2ml, 8.18mmol) was added dropwise to a solution of

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acid **212e** (1.95g, 5.6mmol), (3*S*, 2*S*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett., 2, pp. 615-618 (1992); 1.80g, 6.16mmol) and $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (50mg) in dry CH_2Cl_2 (36ml), with stirring, under dry nitrogen. After 5 min 1-hydroxybenzotriazole (1.51g, 11.2mmol 6.72mmol) was added followed after cooling (ice/ H_2O) by ethyldimethylaminopropyl carbodiimide hydrochloride (1.29g, 6.72mmol). After 5 mins the cooling bath was removed and the mixture was kept at room temperature for 4h, diluted with EtOAc, washed with 1M HCl, brine, sat. aq. NaHCO_3 and brine, dried (MgSO_4) and concentrated. Flash chromatography (silica gel, 0-90% EtOAc in CH_2Cl_2) gave the product as a white solid (2.34g, 78%): IR (KBr) 3499, 1792, 1658, 1536, 1421, 1279, 1257, 1123, 977, 699; ^1H NMR (CDCl_3) δ 7.81 (2H, m), 7.54-7.34 (8H, m), 7.1, 6.97, 6.89, 6.48 (2H, m, d, *J* 7.7, d, *J* = 7.5, d, *J* = 7.6), 5.57, 5.28 (1H, d, *J* = 5.2, s), 5.23-5.07 (2H, m), 4.93-4.42, 3.22-2.70, 2.51-2.26, 2.08-1.69, 1.22 (15H, 5m). Anal. Calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_7 \cdot 0.5\text{H}_2\text{O}$: C, 61.87; H, 5.75; N, 10.32. Found C, 62.02; H, 5.65; N, 10.25.

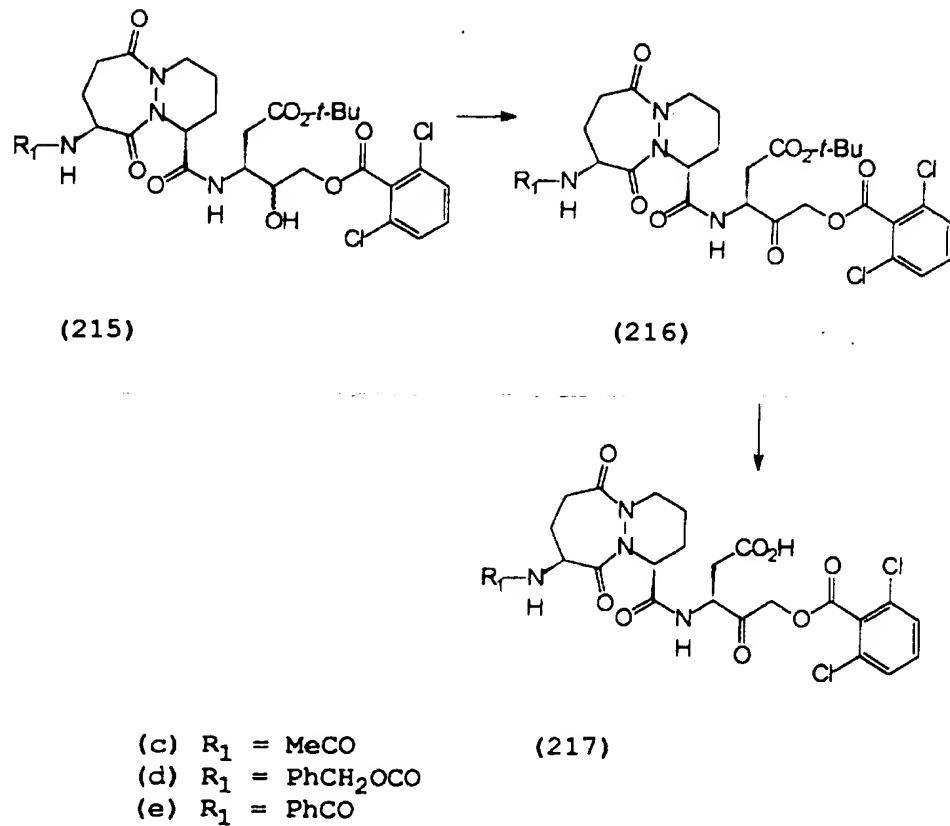
[*3S(1S,9S)*] 3-(9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-25 [1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (**214c**), was synthesized from **213c** by a method similar to the method used to synthesize **214e** from **213e** to provide colourless crystals (140mg, 99%): mp 90-180 °C; $[\alpha]_D^{22} -114$ (c 0.10, MeOH); IR (KBr) 3334, 3070, 2946, 1787, 1658, 1543, 1422, 1277, 1258; ^1H NMR ($\text{d}_6\text{-DMSO}$) δ 8.66 (1H, m), 8.18 (1H, d), 6.76 (1H, s), 5.08 (1H, m), 4.68 (1H, m), 4.30 (1H, m), 2.92-2.70 (2H, m),

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2.27-2.06 (3H, m), 1.95-1.72 (4H, m), 1.85 (3H, s),
1.58 (2H, m); MS(ES -) 381 (M-1, 100%); Accurate mass
calculated for $C_{16}H_{23}N_4O_7$ (MH^+): 383.1567. Found:
383.1548.

- 5 [3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-
diazepine-1-carboxamido)-4-oxobutanoic acid (214e). A
mixture of 213e (2.29g, 4.28mmol), 10% palladium on
carbon (1.8g) and MeOH (160ml) was stirred under H_2 at
10 atmospheric pressure for 6.3h. After filtering and
concentrating the hydrogenation was repeated with fresh
catalyst (1.8g) for 5h. After filtering and
concentrating the residue was triturated with diethyl
ether, filtered and washed well with ether to give 214e
15 as a white solid (1.67g, 88%): mp 143-147 °C; $[\alpha]_D^{23}$ -
125 ° (c 0.2, CH₃OH). IR (KBr) 3391, 1657, 1651, 1538,
1421, 1280, 1258; ¹H NMR (CD₃OD) δ 7.90 (2H, m), 7.63-
7.46 (3H, m), 5.25 (1H, m), 5.08-4.85 (1H, m), 4.68-
4.53 (2H, m), 4.33-4.24 (1H, m), 3.62-3.44, 3.22-3.11,
20 2.75-2.21, 2.15-1.92, 1.73-1.66 (11H, 5m). Anal. Calcd
for $C_{21}H_{24}N_4O_7$ H₂O: C, 54.54; H, 5.67; N, 12.11. Found
C, 54.48; H, 5.63; N, 11.92.

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[3S,4RS(1S,9S)] t-Butyl 3-[9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-hydroxypentanoate (**215c**), was synthesized from **214c** by the same method as compound **215e**, to afford a mixture of diastereomers as a white glassy solid (398mg, 84%): IR (KBr) 3338, 2977, 1738, 1658, 1562, 1541, 1433, 1368, 1277, 1150; ¹H NMR (CDCl₃) δ 7.36-7.32 (3H, m), 6.91 (1H, d), 6.30 (1H, d), 5.15-5.09 (1H, m) 5.01-4.88 (1H, m), 4.61-4.44 (2H, m), 4.37-4.08 (3H, m), 3.32-3.18 (1H, m), 3.04-2.89 (1H, m), 2.82-2.51 (4H, m), 2.39-2.29 (1H, m), 2.08-1.64 (4H, m) 2.02 (3H, s); Anal. Calcd for

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$C_{28}H_{34}N_4Cl_2O_9$: C, 52.26; H, 5.64; N, 8.71. Found: C, 52.44; H, 5.87; N, 8.16. MS (ES -) 645/3/1 (M-1, 26%), 189 (81), 134 (100). Accurate mass calculated for $C_{28}H_{37}N_4Cl_2O_9$ (MH^+): 643.1938. Found: 643.1924.

5 Accurate mass calculated for $C_{28}H_{36}N_4Cl_2O_9Na$ (MNa^+) 665.1757. Found: 665.1756.

- [3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzylloxy)-4-hydroxypentanoate (215d), was synthesized from 214d by the same method as compound 215e to afford a mixture of diastereomers (657mg, 70%) as a glassy white solid: IR (KBr) 3420, 3361, 2975, 2931, 1716, 1658, 1529, 1434, 1367, 1348, 1250, 1157, 1083, 1055; 1H NMR ($CDCl_3$) δ 7.32 (8H, m), 7.14 (1H, d), 5.81 (1H, d), 5.15 (1H, m), 5.07 (2H, s), 4.74-4.65 (1H, m), 4.58-4.22 (4H, m), 4.15-4.06 (1H, m), 3.72 (1H, m), 3.32-3.21 (1H, m), 3.04-2.94 (1H, m), 2.69-2.52 (3H, m), 2.33-2.27 (1H, m), 1.95-1.59 (4H, m), 1.28 (9H, s); Anal. Calcd for $C_{34}H_{40}N_4Cl_2O_{10}$ ·0.5 H_2O : C, 54.70; H, 5.54; N, 7.50. Found: C, 54.98; H, 5.59; N, 7.24. MS (ES -) 737/5/3 (M-1, 22%), 193/1/89 (100). Accurate mass calculated for $C_{34}H_{41}N_4Cl_2O_{10}$ (MH^+) 735.2120. Found: 735.2181.
- 25 [3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzylloxy)-4-hydroxypentanoate (215e), Tributyltin hydride (4.6ml; 11.4mmol) was added dropwise to a stirred mixture of (3*S*,4*RS*) t-Butyl (N-allyloxycarbonyl)-3-amino-5-(2,6-dichlorobenzoyloxy)-4-

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hydroxypentanoate (prepared by a method similar to the method described in Revesz et al., *Tetrahedron Lett.*, 35, pp. 9693-9696 (1994)) (2.64g; 5.7mmol), $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (50mg), CH_2Cl_2 (100ml) and DMF (20ml) at room temperature. The mixture was stirred for a further 10min was then 1-hydroxybenzotriazole (1.54g, 11.4mmol) was added. The mixture was cooled to 0 °C then ethyldimethylaminopropyl carbodiimide hydrochloride (1.31g; 6.84mmol) added. The mixture was kept at this temperature for 15min then at room temperature for 17h. The mixture was diluted with EtOAc (300ml), washed with 1M HCl (2x100ml), sat. aq. NaHCO_3 (3x100ml) and brine (2x100ml), dried (MgSO_4) and concentrated. The residue was purified by flash chromatography (2-5% (MeOH/ CH_2Cl_2) to afford 3.24g (81%) of **215e** as a glassy solid: mp 106-110 °C; IR (KBr) 3354, 1737, 1659, 1531, 1433, 1276, 1150; ^1H NMR (CDCl_3) δ 7.80 (2H, dd, J = 7.9 and 1.5), 7.75-7.26 (6H, m), 7.14-6.76 (2H, m), 5.30-5.02 (2H, m), 4.63-4.11 (5H, m), 3.44-3.26 (2H, m), 3.10-2.30 (5H, m), 2.10-1.60 (5H, m), 1.44 (9H, s); Anal. Calcd for $\text{C}_{33}\text{H}_{38}\text{Cl}_2\text{N}_4\text{O}_9 \cdot 0.75\text{H}_2\text{O}$: C, 55.12; H, 5.54; N, 7.79; Cl, 9.86. Found: C, 55.04; H, 5.34; N, 7.80; Cl, 10.24. MS (ES +) 709/7/5 (M + 1), 378 (59), 324 (64), 322 (100).

[*3S(1S,9S)*] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (**216c**), was synthesized from **215c** by the same method as compound **216e** as a glassy white solid (300mg, 83%): mp 80-125 °C; $[\alpha]_D^{23} -89.1$ (c 1.08, CH_2Cl_2); IR (KBr) 3356, 2979, 2935, 1740, 1659, 1532,

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1434, 1369, 1276, 1260, 1151; ^1H NMR (CDCl_3) δ 7.39-
7.32 (3H, m), 7.13 (1H, d), 6.34 (1H, d), 5.22-5.17
(1H, m), 5.11 (1H, d), 5.04 (1H, d), 4.99-4.88 (2H, m),
4.64-4.52 (1H, m), 3.29-3.11 (1H, m), 3.05-2.67 (4H,
5 m), 2.39-2.29 (1H, m), 2.02 (3H, s), 1.98-1.75 (4H, m),
1.46 (9H, s); Anal. Calcd for $\text{C}_{28}\text{H}_{34}\text{N}_4\text{Cl}_2\text{O}_9$: C, 52.42;
H, 5.34; N, 8.73. Found: C, 52.53; H, 5.70; N, 7.85.
MS (ES-) 643/41/39 (M-1, 100%). Accurate mass
calculated for $\text{C}_{28}\text{H}_{35}\text{N}_4\text{Cl}_2\text{O}_9$ (MH^+): 641.1781. Found:
10 641.1735. Accurate mass calculated for $\text{C}_{28}\text{H}_{34}\text{N}_4\text{Cl}_2\text{O}_9\text{Na}$
(Mna^+): 663.1601. Found: 663.1542.

[3S(1S,9S)] t-Butyl 3-(9-benzyloxycarbonylamino-6,10-
dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-
15 dichlorobenzoyloxy)-4-oxopentanoate (216d), was
synthesized from 215d by the same method as compound
216e to afford 216d as a white glassy solid (688mg,
68%): mp 90-170 °C; $[\alpha]_D^{25} -83.4$ (c 1.01, CH_2Cl_2); IR
(KBr) 3338, 2933, 1736, 1670, 1525, 1433, 1417, 1368,
20 1258, 1151, 1056, 1031; ^1H NMR (CDCl_3) δ 7.33 (8H, m),
7.18 (1H, d), 5.65 (1H, d), 5.19 (1H, m), 5.09 (2H, s),
4.98-4.86 (1H, m), 4.82-4.49 (2H, d), 3.30-3.07 (1H,
m), 3.05-2.59 (4H, m), 2.42-2.27 (1H, m), 2.18-1.59
(5H, m), 1.42 (9H, s); MS (ES-) 737/5/3 (M, 13%), 185
25 (100).

[3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-
dichlorobenzoyloxy)-4-oxopentanoate (216e). Dessa-
30 Martin reagent (3.82g; 9.0mmol) was added to a stirred
solution of the alcohol 215e (3.17g; 4.5mmol) in

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CH₂Cl₂ (100ml). The mixture was stirred for 1h, diluted with EtOAc (300ml), then washed with a 1:1 mixture of sat. Na₂S₂O₃ and sat. NaHCO₃ (100ml) followed by brine (100ml). The mixture was dried (MgSO₄) then concentrated. The residue was purified by flash chromatography to afford 2.2g (70%) of **216e** as a colourless solid: mp 102-107 °C; [α]_D³² -82.5 (c 0.1, CH₂Cl₂); IR (KBr) 3374, 2937, 1739, 1661, 1525, 1433, 1275, 1260, 1152; ¹H NMR (CDCl₃) δ 7.85-7.78 (2H, m), 7.57-7.32 (6H, m), 7.09 (1H, d, J = 7.9), 7.01 (1H, d, J 7.3), 5.25-5.16 (1H, m), 5.16-5.05 (1H, m), 5.15 (1H, d), 5.03 (1H, d), 4.99-4.90 (1H, m), 4.68-4.54 (1H, m), 3.31-3.17 (1H, m), 3.17-2.72 (4H, m), 2.45-2.35 (1H, m), 2.30-1.66 (5H, m), 1.44 (9H, s); Anal. Calcd for C₃₃H₃₆Cl₂N₄O₉. 0.5H₂O: C, 55.62; H, 5.23; N, 7.86; Cl, 9.95. Found: C, 55.79; H, 5.15; N, 7.80; Cl 9.81. MS (ES +) 729/7/5 (M + Na), 707/5/3 (M + 1), 163 (100%).

[3S(1S,9S)] 3-(9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-1,2-a)[1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (**217c**), was synthesized from **216c** by the same method as compound **217e** as a glassy white solid (166mg, 66%): mp 85-175 °C; [α]_D²⁵ -156 (c 0.13, MeOH); IR (KBr) 3373, 2929, 1742, 1659, 1562, 1533, 1433, 1412, 1274, 1266, 1223, 1197, 1145, 1138; ¹H NMR (CD₃OD) δ 7.38 (3H, s), 5.14-5.03 (1H, m), 4.49-4.32 (2H, m), 3.50-3.27 (1H, m), 3.11-2.92 (1H, m), 2.84-2.62 (2H, m), 2.46-2.11 (2H, m), 2.05-1.46 (5H, m), 1.92 (3H, s); Anal. Calcd for C₂₄H₂₆N₄Cl₂O₉.H₂O: C, 47.77; H, 4.68; N, 9.29. Found: C, 47.75; N, 4.59; N, 9.07. MS (ES +) 627/5/3 (M+K, 21%), 611/9/7 (M+Na, 87), 589/7/5 (M⁺ +1, 71),

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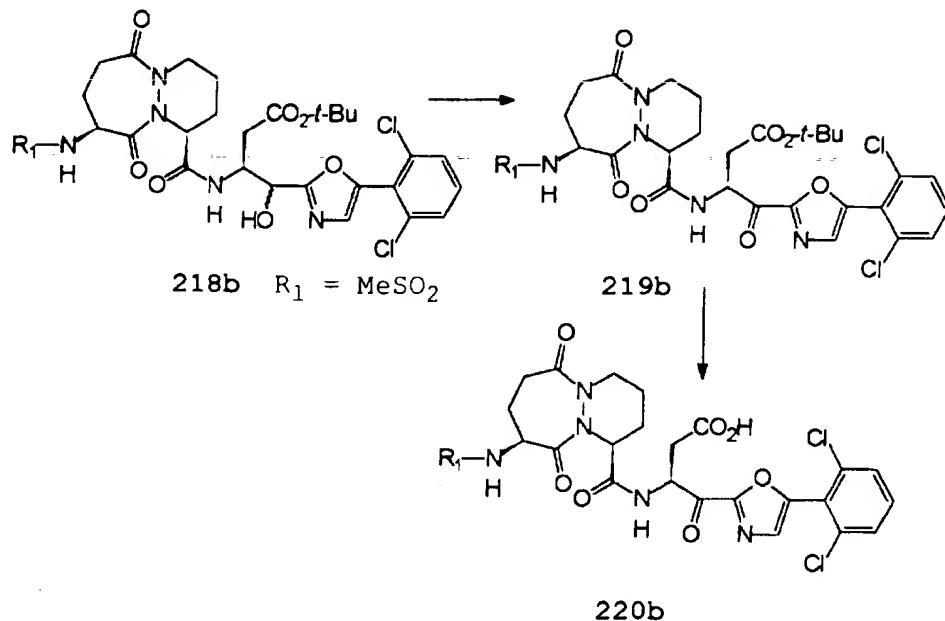
266 (100); Accurate mass calculated for $C_{24}H_{27}N_4Cl_2O_9$ (MH^+): 585.1155. Found: 585.1134.

[3S(1S,9S)] 3-(9-Benzylloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-5-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217d), was synthesized from 216d by the same method as compound 217e to afford 217d as a white glassy solid (310mg, 96%): mp 85-110 °C; $[\alpha]_D^{24}$ -85.9 (c 0.13, MeOH); IR (KBr) 3351, 2945, 1738, 1669, 1524, 1433, 1258, 1147, 1057; 1H NMR (CD_3OD) δ 7.56 (4H, m), 7.45 (5H, m), 5.32 (2H, m), 5.20 (2H, s), 4.76-4.48 (3H, m), 3.65-3.38 (3H, m), 3.27-3.09 (2H, m), 3.03-2.89 (2H, m), 2.65-2.24 (3H, m), 2.19-1.62 (5H, m); MS (ES -) 679/7/5 (M-1, 100%); Accurate mass calculated for $C_{30}H_{31}N_4Cl_2O_{10}$ (MH^+): 677.1417. Found: 677.1430.

[3S(1S,9S)] 3-(9-Benzylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-5-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217e), TFA (25ml) was added dropwise to an ice cold stirred solution of the ester 216e (2.11g, 3.0mmol). The mixture was stirred at 0 °C for 20min then at room temperature for 1h. The mixture was evaporated to dryness then coevaporated with ether three times. Addition of dry ether (50 ml) and filtration afforded 1.9g (98%) of 217e as a colourless solid: mp 126-130 °C; $[\alpha]_D^{30}$ -122.0 (c 0.1, MeOH); IR (KBr) 3322, 1740, 1658, 1651, 1532, 1433, 1277, 1150; 1H NMR (D_6 -DMSO) δ 8.87 (1H, d, J = 7.4), 8.61 (1H, d, J = 7.8), 7.92-7.86 (2H, m), 7.65-7.43 (6H, m), 5.25-5.12 (3H, m), 4.94-4.60 (2H, m), 4.44-4.22 (1H, m),

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3.43-3.10 (1H, m), 3.00-2.52 (3H, m), 2.45-2.10 (3H, m), 2.10-1.75 (2H, m), 1.75-1.50 (2H, m); Anal. Calcd for C₂₉H₂₈Cl₂N₄O₉. 1H₂O: C, 52.34; H, 4.54; N, 8.42; Cl, 10.66. Found: C, 52.02; H, 4.36; N, 8.12; Cl, 10.36. MS (ES -) 649/7/5 (M - 1), 411 (100%).



[3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 4-[5-(2,6-dichlorophenyl)-oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxybutanoate (218b), was prepared from the acid 212b and 99 in an analogous way to compound 215e to afford a mixture of diastereomers (865mg, 80%) as a colourless solid: IR 10 15 (KBr) 3298, 2974, 1723, 1659, 1544, 1518, 1430, 1394, 1370, 1328, 1273, 1256, 1156, 1134; ¹H NMR (CDCl₃) δ 7.45-7.28 (4H, m), 7.26-7.15 (2H, m), 5.26-5.10 (2H, m), 4.80-4.67 (1H, m), 4.59-4.42 (2H, m), 3.32-3.17 (1H, m), 2.96 (3H, 2xs), 2.93-2.79 (1H, m), 2.71-2.53

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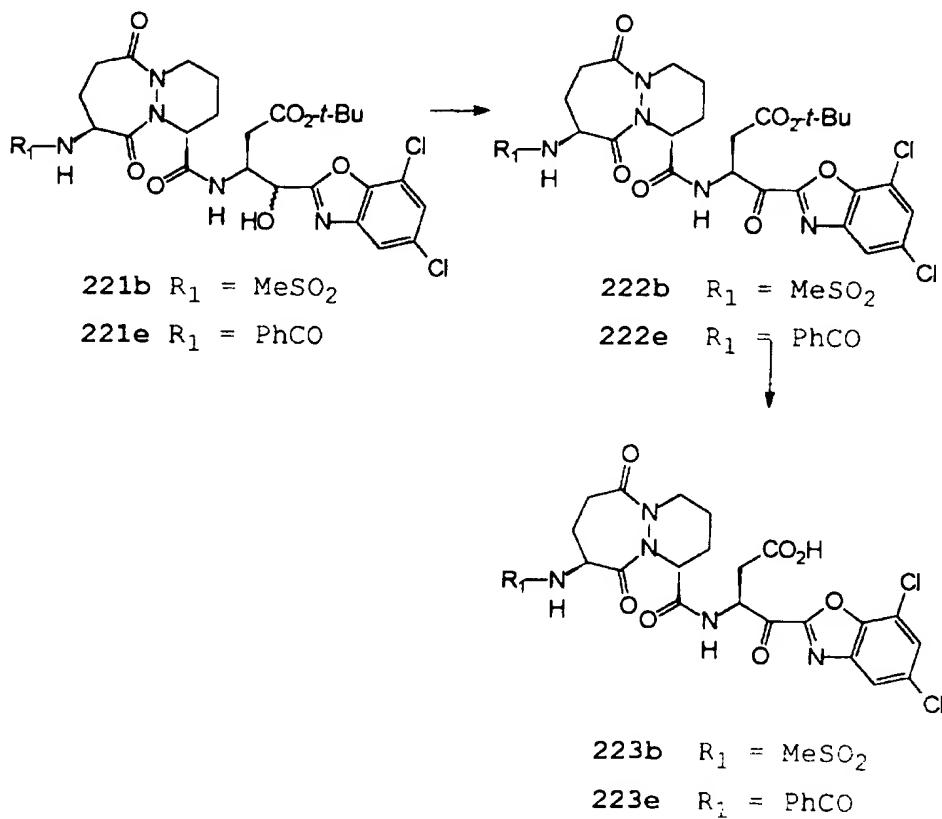
(4H, m), 2.38-2.28 (1H, m), 2.07-1.81 (4H, m); Anal. Calcd for C₂₈H₃₅N₅Cl₂O₉S. 0.5 H₂O: C, 48.21; H, 5.20; N, 10.03. Found: C, 48.35; H, 5.26; N, 9.48. MS (ES+) 714/2/0 (M + Na, 25%), 692/90/88 (M⁺ + 1, 51), 636/4/2 (38), 246 (100). Accurate mass calculated for C₂₈H₃₆N₅Cl₂O₉S (MH⁺): 688.1611. Found: 688.1615.

[3S(1S,9S)]t-Butyl 4-[5-(2,6-dichlorophenyl)-oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoate (219b), was prepared from 218b in an analogous way to compound 216e as an off-white powder (675mg, 81%): mp 100-200 °C; [α]_D²⁴ -84.9 (c 1.01, CH₂Cl₂); IR (KBr) 3336, 2978, 2936, 1719, 1674, 1510, 1433, 1421, 1369, 1329, 1274, 1257, 1155, 991, 789; ¹H NMR (CDCl₃) δ 7.47-7.38 (4H, m), 7.24 (1H, d), 5.61-5.53 (1H, m), 5.48 (1H, d), 5.38-5.30 (1H, m), 4.67-4.45 (2H, m), 3.48-3.18 (2H, m), 3.04-2.90 (2H, m), 2.97 (3H, s), 2.69-2.54 (1H, m), 2.42-2.32 (1H, m), 2.22-2.15 (1H, m), 2.07-1.93 (3H, m), 1.71-1.65 (2H, m), 1.38 (9H, s); Anal. Calcd for C₂₈H₃₃N₃Cl₂O₉S: C, 48.98; H, 4.84; N, 10.20; S, 4.67. Found: C, 48.73; H, 4.95; N, 9.65; S, 4.54. MS (ES+) 692/90/88 (M⁺ + 1, 100%), 636/4/2 (71). Accurate mass calculated for C₂₈H₃₄N₅Cl₂O₉S (MH⁺): 686.1454. Found: 686.1474.

[3S(1S,9S)] 4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (220b), was prepared from 219b in an analogous way to compound 217e as a pale cream powder (396mg, 87%): mp 100-200 °C; [α]_D²⁷ -

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129 (c 0.12, MeOH); IR (KBr) 3310, 3153, 1713, 1667,
 1557, 1510, 1432, 1421, 1329, 1273, 1258, 1221, 1193,
 1153, 1134, 992, 789; ^1H NMR (d^6 DMSO) δ 7.88 (1H, s),
 7.81-7.60 (4H, m), 5.49-5.28 (1H, m), 5.24-5.14 (1H,
 5 m), 4.46-4.22 (2H, m), 3.30-3.03 (2H, m), 2.97-2.76
 (3H, m), 2.96 (3H, s), 2.46-2.24 (1H, m), 2.16-2.05
 (1H, m), 2.03-1.78 (3H, m), 1.68-1.46 (2H, m); MS (ES-)
 632/30/28 (M - 1, 68%), 149/7/5 (100). Accurate mass
 calculated for $\text{C}_{24}\text{H}_{26}\text{N}_5\text{Cl}_2\text{O}_9\text{S}$ (MH^+): 630.0828. Found:
 10 630.0852.



15 [3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 4-(5,7-dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-

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[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxybutanoate (221b), was prepared from the acid 212b and (3S,4RS) t-butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204) by an analogous

5 method as that used for compound 215e to afford a mixture of diastereomers (460mg, 70%) as a glass: IR (film) 3325, 1725, 1664, 1453, 1399, 1373, 1327, 1274, 1256, 1155; ¹H NMR (CDCl₃) δ 7.57 (1H, m), 7.36 (2H, m), 6.06 (1H, t), 5.29 (2H, m), 4.79 (1H, m), 4.47 (1H, m), 3.23 (1H, m), 2.97 and 2.94 (3H combined, 2 x s), 2.9-2.4 (4H, m), 2.30 (1H, m), 1.96 (4H, m), 1.41 and 1.37 (9H combined, 2 x s). MS ES Da/e 660 (M - 1)⁺ Cl³⁵ 100%, 662 (M - 1)⁺ Cl³⁷.

[3S,4RS(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-

15 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-hydroxybutanoate (221e), was prepared from the acid (212e) and (3S,4RS) t-butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204) by an analogous method as that used for compound 215e to afford a mixture of diastereomers (613mg, 87%) as a glass: IR (film) 3328, 1729, 1660, 1534, 1454, 1422, 1399, 1276, 1254, 1155; ¹H NMR (CDCl₃) δ 7.80 (2H, d), 7.60-7.35 (5H, m), 7.05 (2H, m), 5.13 (3H, m), 4.74 (1H, m), 4.51 (1H, m), 3.25 (1H, m), 3.1-2.6 (5H, m), 2.33 (1H, m), 2.1-1.5 (5H, m), 1.43 and 1.41 (9H combined, 2 x s). MS ES⁺ Da/e 688 (M + 1)⁺ Cl³⁵ 55%, 690 (M + 1)⁺ Cl³⁷ 35%, 328 100%.

30 [3S(1S,9S)]t-Butyl 4-(5,7-dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-

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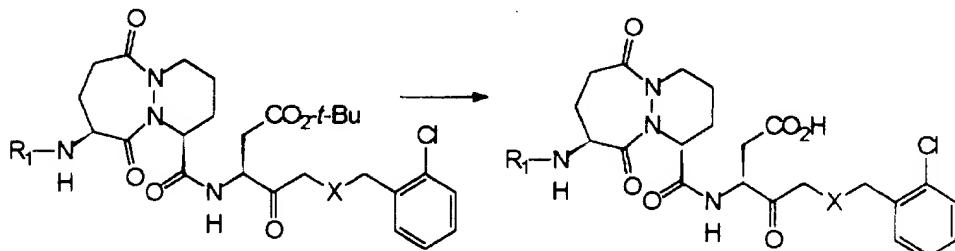
octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoate (222b), was prepared from 221b by an analogous method as that used for compound 216e to afford a colourless glass (371mg, 86%): $[\alpha]_D^{26}$ 5 -81.0 (c 0.1, CH_2Cl_2); IR (KBr) 3324, 2979, 2936, 1726, 1664, 1394, 1370, 1328, 1155, 991; ^1H NMR (CDCl_3) δ 7.78 (1H, d), 7.57 (2H, m), 5.87 (1H, d), 5.69 (1H, m), 5.47 (1H, m), 4.55 (2H, m), 3.24 (2H, m), 3.0 (5H, m + s), 2.59 (1H, m), 2.39 (1H, m), 2.2 - 1.7 (4H, m), 1.65 10 (1H, m), 1.40 (9H, s).

[3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxobutanoate (222e), was prepared from 221e by an analogous method as that used for compound 216e to afford a colourless glass (480mg, 84%): $[\alpha]_D^{25}$ -86.4 ° (c 0.1 CH_2Cl_2); IR (KBr) 3337, 2978, 2938, 1728, 1657, 1534, 1456, 1422, 1395, 1370, 1277, 1250, 1154; ^1H NMR (CDCl_3) δ 7.80 (3H, m), 7.50 15 (4H, m), 7.20 (1H, d), 7.02 (1H, d), 5.60 (1H, m), 5.28 (1H, m), 5.15 (1H, m), 4.11 (1H, m), 3.34 (2H, m), 2.96 (3H, m), 2.40 (1H, m), 2.20 (1H, m), 1.92 (2H, m), 1.67 (2H, m), 1.38 (9H, s). MS ES⁻ Da/e 684 (M - 1)⁻ Cl³⁵ 47%, 686 (M - 1)⁻ Cl³⁷ 32%.
25 **[3S(1S,9S)] 4-(5,7-Dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (223b)**, was prepared from 222b by an analogous method as that used for compound 217e to afford an off-white solid (257mg, 78%): $[\alpha]_D^{25}$ -105.7 ° (c 0.1, CH_2Cl_2); IR (KBr) 3321,

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1723, 1663, 1407, 1325, 1151, 992; ^1H NMR (D_6 -DMSO) δ 8.96 (1H, d), 8.18 (1H, d), 7.96 (1H, d), 5.50 (1H, m), 5.15 (1H, m), 4.30 (2H, m), 3.06 (2H, m), 2.87 (5H, m + s), 2.29 (1H, m), 1.99 (4H, m), 1.56 (2H, m).

5 [3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxobutanoic acid (223e), was prepared from 222e by an analogous method as that used
10 for compound 217e to afford a pale cream solid (311mg, 78%): mp 167-180 °C; $[\alpha]_D^{23} -88.6$ ° (c 0.1 CH_2Cl_2); IR (KBr) 3331, 1724, 1658, 1534, 1458, 1421, 1279, 1256, 991; ^1H NMR (CDCl_3) δ 7.77 (4H, m), 7.4 (5H, m), 5.57 (1H, bs), 5.33 (1H, bs), 5.47 (1H, q), 4.56 (1H, bd),
15 3.60 (2H, m), 3.20 (3H, m), 2.76 (1H, m), 2.36 (1H, dd), 2.0 (3H, m), 1.66 (1H, m). MS ES Da/e 628 (M - 1) $^-$ Cl 35 7%, 630 (M - 1) $^-$ Cl 37 2.3%, 584 100%.



224e $R_1 = \text{PhCO}$, $X = \text{S}$

225e $R_1 = \text{PhCO}$, $X = \text{O}$

226e $R_1 = \text{PhCO}$, $X = \text{S}$

227e $R_1 = \text{PhCO}$, $X = \text{O}$

20 [3*S*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenyl)methylthio-4-oxopentanoate (224e). 1-Hydroxybenzotriazole (0.23g,

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1.71mmol) and ethyl dimethylaminopropyl carbodiimide hydrochloride was added to a stirred solution of the acid **212e** (0.295g, 0.853mmol) in THF (5ml). After 5min water (0.5ml) was added followed, after a further 7min,
5 by the addition of a solution of (3*S*) t-butyl-3-allyloxycarbonylamino-5-(2-chloro-phenyl)methylthio-4-oxopentanoate (**123**, 0.478g, 1.02mmol) and $(PPh_3)_2PdCl_2$ (20mg) in THF (2ml). Tributyltin hydride (0.65ml, 2.33mmol) was added dropwise during 20min. The mixture
10 was kept for 4.5h then diluted with EtOAc, washed with 1M HCl, brine, sat. aq. $NaHCO_3$ and then brine again. The mixture was dried ($MgSO_4$) and concentrated. The residue was triturated several times with hexane, which was decanted and discarded, then purified by flash
15 chromatography (10-100% EtOAc in CH_2Cl_2) to afford 0.2g (35%) of a white glassy solid: mp 70-72 °C; $[\alpha]_D^{26}$ - 82.5 ° (c 0.02, CH_2Cl_2). IR (KBr) 3404, 1726, 1660, 1534, 1524, 1422, 1277, 1254, 1154; 1H NMR ($CDCl_3$) δ 7.83-7.78 (2H, m), 7.7, 7.75-7.32, 7.26-7.20 (7H, 3m),
20 7.12 (1H, d, J = 8.2), 7.01 (1H, d, J = 7.3), 5.23-5.08 (2H, m), 5.03-4.94 (1H, m), 4.62 (1H, dt, J = 14.5), 3.78 (2H, m), 3.38-3.29 (1H, m), 3.26 (2H, s), 3.06-2.82 (4H, m), 2.71 (1H, dd, J = 17.2, 4.5), 2.39 (1H, dd, J = 13.2, 6.5), 2.15-1.83, 1.73-1.63 (5H, m), 1.45
25 (9H, s). Anal. Calcd for $C_{33}H_{39}ClN_4O_7S$: C, 59.05; H, 5.86; N, 8.35. Found: C, 59.00; H, 5.80; N, 7.92.

[*3RS, (1S,9S)*] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenylmethoxy)-4-oxopentanoate (**225e**), was prepared from acid **212e** and (3*S*) t-butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethoxy)-4-oxopentanoate (**201**) using a

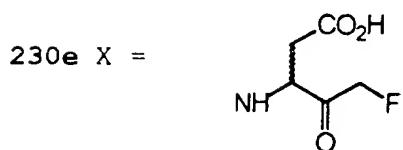
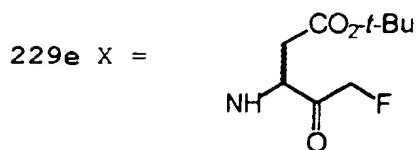
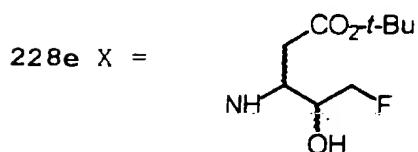
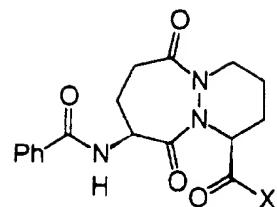
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method similar to that used for compound **224e**, to afford 40mg (23%) of a glassy solid: ^1H NMR (CDCl_3) δ 7.83-7.73 (2H, m), 7.67-7.10 (9H, m), 5.23-5.09 (2H, m), 4.59 (1H, m), 4.45-4.22 (2H, m), 3.7-3.19, 3.08-5 2.72, 2.71-2.47, 2.05-1.85, 1.72-1.61, 1.45-1.26 (20H, 6m).

[*3S(1S,9S)*] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenyl)methylthio-10 4-oxopentanoic acid (**226e**), was prepared from **224e** by an analogous method as that used for compound **217e** which afforded 0.22g (81%) of an off-white solid: mp 95-100 °C; $[\alpha]_D^{23} -95.6^\circ$ (c 0.2, CH_2Cl_2). IR (KBr) 3393, 1720, 1658, 1529, 1422, 1279; ^1H NMR (D_6 -DMSO) δ 15 8.80 (1H, d, $J = 7.5$), 7.89 (2H, m), 7.7 (1H, d, $J = 7.7$), 7.56-7.28 (7H, m), 5.10 (1H, m), 4.87-4.73 (2H, m), 4.39 (1H, m), 3.77 (2H, m), 3.44, 3.35 (2H, + H_2O , 2m), 2.97-2.56, 2.2, 1.92, 1.61 (11H, 4m). Anal. Calcd for $\text{C}_{29}\text{H}_{31}\text{ClN}_4\text{O}_7\text{S}$ 0.5 H_2O : C, 55.02; H, 5.10; N, 8.85. 20 Found: C, 55.00; H, 5.09; N, 8.71.

[*3RS, (1S,9S)*] 3-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenylmethyloxy)-4-oxopentanoic acid (**227e**), was prepared from **225e** by an 25 analogous method as that used for compound **217e**. The product was further purified by flash chromatography (0-5% MeOH/ CH_2Cl_2) to afford 19mg (81%) of a glassy solid: ^1H NMR (CDCl_3) δ 7.79 (2H, m), 7.66-7.18 (9H, m), 5.30-5.10 (2H, m), 4.85 (1H, m), 4.65 (2H, m), 4.53 30 (1H, m), 4.28 (2H, m), 3.28, 3.01, 2.72, 2.33, 1.94, 1.60 (11H, 6m). MS (ES⁻, m/z) 597 ($\text{M}^+ - 1$, 100%).

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[3RS,4RS(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-
 5,1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-
 (228e). 1-Hydroxybenzotriazole (0.23g, 1.68mmol)
 followed by ethyldimethylaminopropyl carbodiimide
 hydrochloride (0.21g, 1.09mmol) were added to a stirred
 solution of the acid 212e (0.29g, 0.84mmol) in CH₂Cl₂
 (3ml) at rt. The mixture was kept for 10min then a
 solution of (3RS,4RS) t-butyl 3-amino-5-fluoro-4-
 hydroxypentanoate (Revesz, L. et al. Tetrahedron Lett.,
 52, pp. 9693-9696 (1994); 0.29g, 1.40mmol) in CH₂Cl₂
 (3ml) was added followed by 4-dimethylaminopyridine

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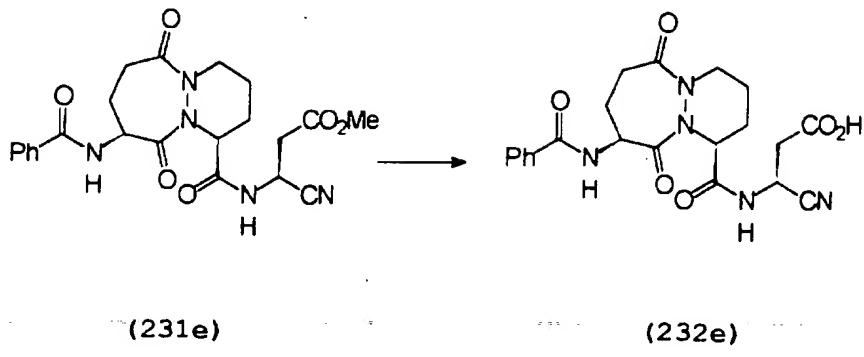
(10mg). The solution was stirred for 17h, diluted with EtOAc, washed with 1M HCl, brine, sat. aq. NaHCO₃ and brine again, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (50-100% EtOAc/CH₂Cl₂ and 5% MeOH/EtOAc) to afford 0.25g (56%) of a white glassy solid: IR (KBr) 3343, 1726, 1658, 1536, 1426, 1279, 1257, 1157; ¹H NMR (CDCl₃) δ 7.84-7.79 (2H, m), 7.57-7.40 (3H, m), 7.05-6.92, 6.73 (2H, 2m), 5.17-5.04 (2H, m), 4.56, 4.35-4.21, 4.04 (5H, 3m), 3.36, 3.09-2.34, 2.00 (11H, 3m), 1.46 (9H, s). Anal. Calcd for C₂₆H₃₅FN₄O₇ 0.5H₂O: C, 57.45; H, 6.65; N, 10.31. Found: C, 57.64; H, 6.56; N, 10.15.

[3RS,4RS(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-oxypentanoate (229e) was prepared from 228c by an analogous method to that used for compound 216e. After purification by flash chromatography (30-50% EtOAc/CH₂Cl₂) the product was obtained as a white glassy solid (0.194g, 89%): IR (KBr) 3376, 1728, 1659, 1529, 1424, 1279, 1256, 1156.

[3RS, (1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-oxopentanoic acid (230e), was prepared from 229e by an analogous method to that used for compound 217e to afford 230e as a white glassy solid (100%): mp 105-125 °C; [α]_D²³ -91.4 ° (c 0.72, CH₃OH). IR (KBr) 3336, 1789, 1737, 1659, 1535, 1426, 1279, 1258, 1186; ¹H NMR (CD₃OD) δ 7.71-7.68 (2H, m), 7.37-7.23 (3H, m), 5.02, 4.88-4.63,

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4.37-4.0 (6H, 3m), 3.30, 2.97, 2.68-2.60, 2.37-1.54
(11H, 4m). MS (ES⁻, m/z) 475 ($M^+ - 1$, 100%).



[3S(1S,9S)]-Methyl 9-(benzoylamino)-3-[6,10-dioxo-
 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-3-cyanopropanoate
 10 (231e). N-Fluorenylmethoxy-carbonyl-3-amino-3-cyanopropionic acid methyl ester (EP0547699A1, 385mg, 1.1mmol) was treated with 17ml of diethylamine. After 1.5h stirring at room temperature the solution was concentrated. The residue was chromatographed on silica gel (3% methanol in CH₂Cl₂) and gave the free amine as a pale yellow oil. To a solution of this oil and hydroxybenzotriazole (297mg, 2.19mmol) in DMF (5ml), was added at 0 °C ethyldimethylaminopropyl carbodiimide (232mg, 1.21mmol, 1.1 equiv) followed by (1S,9S) 9-(benzoylamino)-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (212e). After stirring at 0 °C for 5 min and then at room temperature overnight, the mixture was diluted with CH₂Cl₂ (50ml) and the resulting solution washed successively with 1M HCl (2 x 30ml), H₂O (30ml), 10% NaHCO₃ (2 x 30ml) and sat. aq. NaCl, dried (MgSO₄) and concentrated. Purification by flash

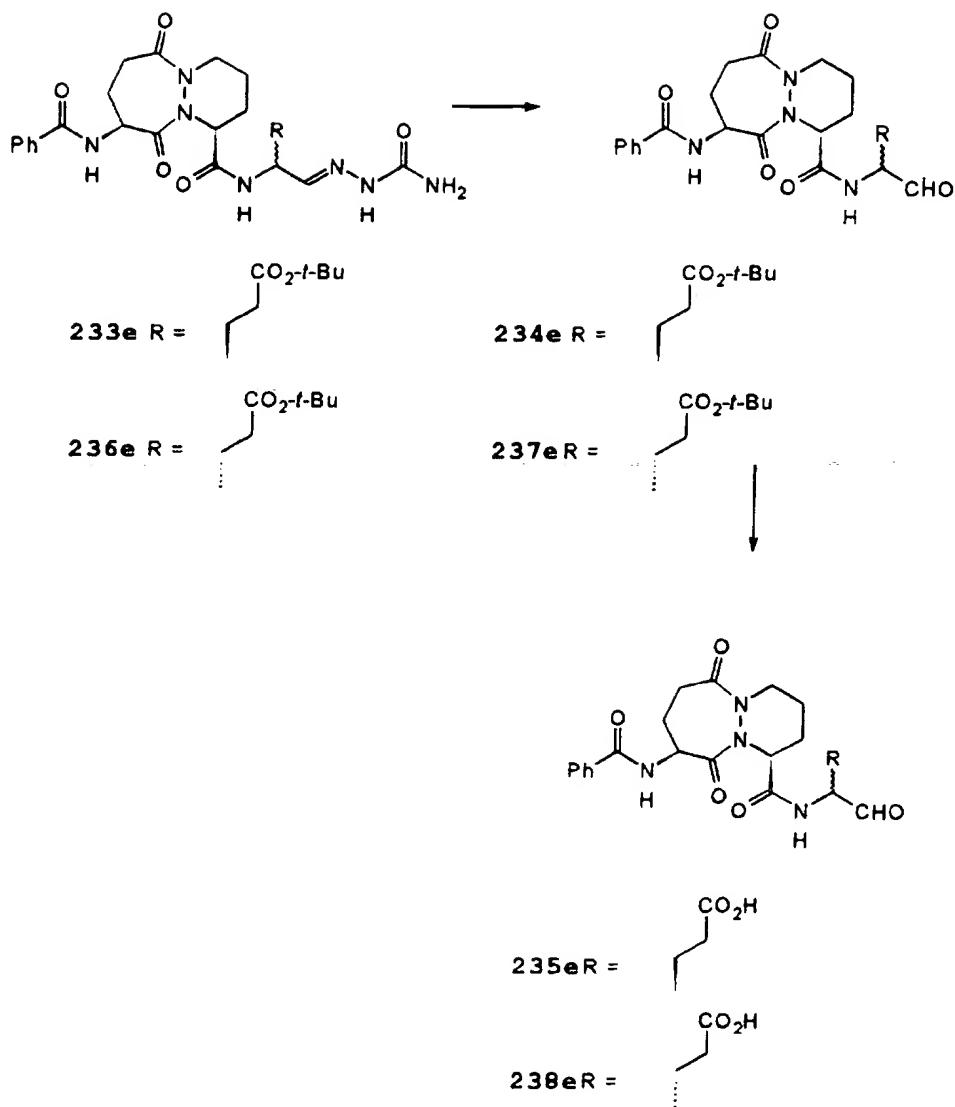
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chromatography on silica gel (3% methanol in CH₂Cl₂) afforded the compound **231e** (404mg, 83%) as a solid: [α]_D²⁰ -121 ° (c 0.14, CH₂Cl₂); ¹H NMR (CDCl₃) δ 7.40-7.83 (5H, m), 7.38 (1H, d), 6.96 (1H, d), 5.27-5.07 (2H, m), 4.66-4.50 (1H, m), 3.79 (3H, s), 3.23-2.73 (6H, m), 2.47-2.33 (1H, m), 2.15-1.82 (4H, m); Anal. Calcd for C₂₂H₂₅N₅O₆: C, 58.0; H, 5.53; N, 15.38. Found: C, 57.6; H, 5.6; N, 15.0.

[3S(1S,9S)] 9-(Benzoylamino)-3-[6,10-dioxo-

- 10 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-3-cyanopropanoic acid (**232e**). A solution of methyl ester **231e** (400mg, 0.88mmol) in methanol (30ml) and water (30ml) was cooled at 0 °C and treated with diisopropylethylamine. 15 The solution was stirred at 0 °C for 10min and then at room temperature overnight. The heterogeneous mixture was concentrated and the solid obtained was chromatographed on silica gel (5% methanol/1% formic acid in CH₂Cl₂) affording the free acid **232e** (170mg, 20 44%) as a white solid: mp 155 °C (dec); [α]_D²⁰ -117 ° (c 0.1, MeOH); IR (KBr) 3343, 3061, 2955, 1733, 1656, 1577, 1533, 1490, 1421, 1342, 1279, 1256, 1222, 1185, 708; ¹H NMR (D⁴-MeOH) δ 7.88-7.28 (5H, m), 5.20-5.03 (1H, m), 4.98-4.84 (2H, m), 4.75-4.53 (1H, m), 4.51-4.34 (1H, m), 3.45-3.22 (1H, m), 3.14-2.94 (1H, m), 3.14-2.94 (1H, m), 2.88-2.61 (2H, m), 2.53-1.50 (8H, m); Anal. Calcd for C₂₁H₂₃N₅O₆ · 1.5H₂O: C, 53.84; H, 5.59; N, 14.95; O, 25.61. Found: C, 54.3; H, 5.4; N, 14.3.

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[4S, (1S,9S)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate semicarbazone (233e). A solution of (1S,9S) 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(benzoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (212e) (345mg, 1.0mmol), (4S) t-butyl N-

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(allyloxycarbonyl)-4-amino-5-oxopentanoate semicarbazone (**208a**) (361mg, 1.1mmol, 1.1 equiv) and $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (20mg) in CH_2Cl_2 (5ml), was treated dropwise with $n\text{-Bu}_3\text{SnH}$ (0.621ml, 2.3mmol, 2.1 equiv).

- 5 The resulting orange brown solution was stirred at 25 °C for 10min and then 1-hydroxybenzotriazole (297mg, 2.2mmol, 2 equiv) was added. The mixture was cooled to 0 °C and ethyldimethylaminopropyl carbodiimide (253mg, 1.3mmol, 1.2 equiv) added. After stirring at 0 °C for 10min and then at room temperature overnight, the mixture was diluted with EtOAc (50ml) and the resulting solution washed successively with 1M HCl (3 x 25ml), 10% NaHCO_3 (3 x 25ml) and sat. aq. NaCl, dried (MgSO_4) and concentrated. Flash chromatography on silica gel 15 (2-10% methanol in CH_2Cl_2) afforded compound **233e** (280mg, 49%) as a tan solid: $[\alpha]_{\text{D}}^{20} -95$ (c 0.09, MeOH); IR (KBr) 3477, 3333, 2968, 2932, 1633, 1580, 1535, 1423, 1378, 1335, 1259, 1156, 1085, 709; ^1H NMR (CDCl_3) δ 9.32 (1H, s), 7.83-7.39 (6H, m), 7.11-7.09 (1H, m), 20 6.30-5.30 (2H, brs), 5.17-5.05 (2H, m), 4.62-4.38 (2H, m), 3.30-3.15 (1H, m), 3.13-2.65 (2H, m), 2.46-2.19 (3H, m), 2.15-1.54 (8H, m), 1.42 (9H, s).

[*4R, (1S,9S)*] *t*-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-

- 25 [1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate semicarbazone (**236e**), was prepared by an analogous method to that used for **233e** using (*4R*) *t*-butyl N-allyloxycarbonyl-4-amino-5-oxo-pentanoate semicarbazone (**208b**, 435mg, 1.33mmol). The product was obtained as a 30 foam (542mg, 71%): $[\alpha]_{\text{D}}^{20} -99$ ° (c 0.19, CHCl_3); IR (KBr) 3473, 3331, 3065, 2932, 2872, 1660, 1580, 1533, 1488, 1423, 1370, 1337, 1278, 1254, 1223, 1155, 1080,

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1024, 983, 925, 877, 846, 801, 770, 705; ^1H NMR (CDCl_3)
δ 9.42 (1H, s), 7.81 (2H, d), 7.51-7.40 (4H, m), 7.06
(1H, d), 6.50-5.50 (2H, broad s), 5.25-5.00 (2H, m),
4.60-4.45 (2H, m), 3.15-2.85 (2H, m), 2.75-2.35 (1H,
5 m), 2.30-1.23 (11H, m), 1.42 (9H, s).

[4S, (1S,9S)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate
(234e). A solution of semicarbazone 233e (390mg,
10 0.68mmol) in methanol (10ml) was cooled at 0 °C and
then treated with a 38% aq. solution of formaldehyde
(2ml) and 1M HCl (2ml). The reaction mixture was then
stirred overnight at room temperature. The solution
was concentrated to remove the methanol. The aq.
15 solution was extracted with EtOAc (30ml). The organic
solution was successively washed with 10% NaHCO_3 (30ml)
and sat. aq. NaCl (30ml), dried (MgSO_4) and
concentrated. Purification by flash chromatography on
silica gel (2-5% methanol in CH_2Cl_2) afforded 234e
20 (179mg, 51%) as a white foam: $[\alpha]_D^{20} -101^\circ$ (c 0.064,
MeOH); IR (KBr) 3346, 2976, 2934, 1730, 1657, 1535,
1456, 1425, 1278, 1255, 1156, 708; ^1H NMR (CDCl_3) δ
9.56 (1H, s), 7.88-7.38 (5H, m), 7.01 and 6.92 (2H,
2d), 5.27-5.08 (2H, m), 4.69-4.46 (1H, m), 3.50-3.27
25 (2H, m), 3.15-2.73 (2H, m), 2.46-1.83 (10H, m), 1.45
(9H, s).

[4R, (1S,9S)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate
30 (237e), was prepared from 236e by an analogous method
to 234e to afford a white foam (390mg, 85%): $[\alpha]_D^{20}$

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-113 ° (c 0.242, CHCl₃); IR (KBr) 3352, 3065, 2974, 1729, 1657, 1536, 1489, 1454, 1423, 1369, 1338, 1278, 1255, 1223, 1156, 1078, 1026, 981, 846, 709.

[4S, (1S,9S)] 4-[9-(Benzoylamino)-6,10-dioxo-

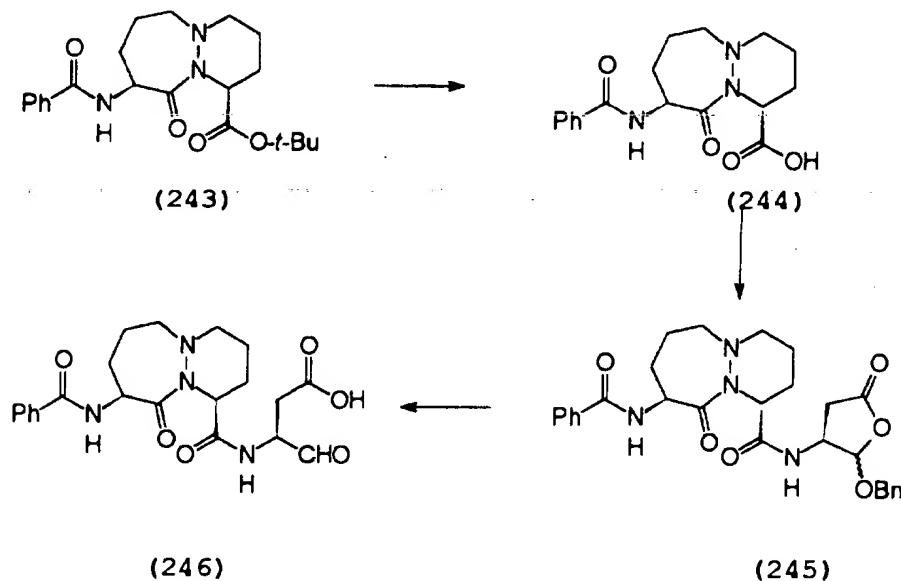
5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoic acid (235e). A solution of t-butyl ester 234e (179mg, 0.35mmol) in dry CH₂Cl₂ (3ml) was cooled to 0 °C and treated with trifluoroacetic acid (2ml). The resulting 10 solution was stirred at 0 °C for 30min and then at room temperature for 2h. The solution was concentrated, the residue taken up in dry CH₂Cl₂ (5ml) and the mixture again concentrated. This process was repeated once again with more CH₂Cl₂ (5ml). The residue obtained was 15 crystallized in diethyl ether. The precipitate was collected and purified on silica gel column (5% methanol in CH₂Cl₂) which afforded compound 235e as a white solid (111mg, 70%): mp 142 °C (dec); [α]_D²⁰ -85.5 (c 0.062, MeOH); IR (KBr) 3409, 3075, 2952, 1651, 1541, 20 1424, 1280, 1198, 1136, 717; ¹H NMR (D₆-DMSO) δ 9.40 (1H, s), 8.62 (2H, m), 7.96-7.38 (5H, m), 5.19-5.02 (1H, m), 4.98-4.79 (1H, m), 4.48-4.19 (1H, m), 3.51-3.11 (2H, m), 3.04-2.90 (2H, m), 2.38-1.46 (10H, m).

[4R, (1S,9S)] 4-[9-(Benzoylamino)-6,10-dioxo-

25 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoic acid (238e), was prepared from 237e by an analogous route to 235e which afforded a beige foam (190mg, 60%): [α]_D²⁰ -78 (c 0.145, MeOH); IR (KBr) 3400, 3070, 2955, 30 2925, 2855, 1653, 1576, 1541, 1490, 1445, 1427, 1342, 1280, 1258, 1205, 1189, 1137, 1075, 1023, 983, 930,

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878, 843, 801, 777, 722; ^1H NMR ($\text{D}_6\text{-DMSO}$) δ 9.40 (1H, s), 8.72-8.60 (2H, m), 7.89 (2H, d), 7.56-7.44 (3H, m), 5.17 (1H, m), 4.90-4.83 (1H, m), 4.46-4.36 (1H, m), 4.20-4.15 (1H, m), 3.40-3.30 (1H, m), 2.98-2.90 (2H, m), 2.50-1.60 (10H, m).



(1*S*,9*S*) t-Butyl 9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (243),

10 was prepared from (1*S*,9*S*) t-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (Attwood, et al. *J. Chem. Soc., Perkin 1*, pp. 1011-19 (1986)), by the method described for **211e**, to afford 2.03g (86%) of a colourless foam: $[\alpha]_D^{25} -15.9^\circ$ (c 15.0, CH_2Cl_2); IR (KBr) 3400, 2976, 2937, 1740, 1644, 1537, 1448, 1425, 1367, 1154; ^1H NMR (CDCl_3) δ 7.88-7.82 (2H, m), 7.60-7.38 (4H, m), 5.48 (1H, m), 4.98 (1H, m), 3.45 (1H, m), 3.22-2.96 (2H, m), 2.64 (1H, m), 2.43-2.27 (2H, m), 1.95 (2H, m), 1.82-1.36 (4H, m), 1.50 (9H, s); Anal. Calcd for $C_{21}\text{H}_{29}\text{N}_3\text{O}_4 \cdot 0.25\text{H}_2\text{O}$: C,

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64.35; H, 7.59; N, 10.72. Found: C, 64.57; H, 7.43; N, 10.62. MS (ES +, m/z) 388 (100%, M⁺ + 1).

(1S,9S) 9-Benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid

5 **(244)**, was prepared from (1S,9S) t-butyl 9-benzoylamino-octahydro-10-oxo-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (**243**), by the method described for **212e**, to afford 1.52g (89%) of a white powder: mp. 166-169 °C (dec); [α]_D²⁵ -56.4 ° (c 10 0.5, CH₃OH); IR (KBr) 3361, 2963, 2851, 1737, 1663, 1620, 1534, 1195, 1179; ¹H NMR (D₆-DMSO) δ 12.93 (1H, brs), 8.44 (1H, d, J = 8.4), 7.93 (2H, m), 7.54 (3H, m), 5.46 (1H, m), 4.87 (1H, m), 3.12 (2H, m), 2.64 (1H, m), 2.64 (1H, m), 2.27 (1H, m), 1.98-1.68 (7H, m), 1.40 (1H, m); Anal. Calcd for C₁₇H₂₁N₃O₄. 0.25H₂O: C, 60.79; H, 6.45; N, 12.51. Found: C, 61.07; H, 6.35; N, 12.55. MS (ES+, m/z) 332 (58%, M⁺ + 1), 211 (100).

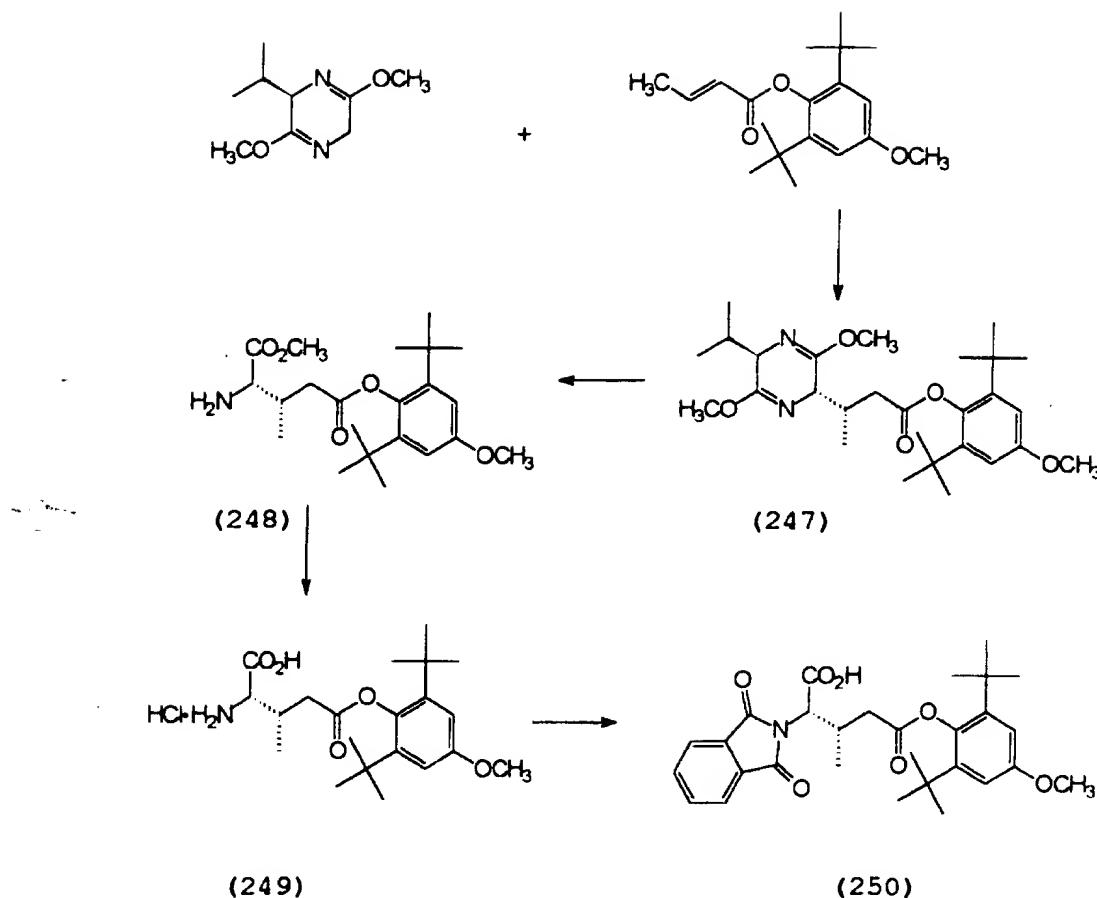
[3S,2RS(1S,9S)] N-(2-Benzylxy-5-oxotetrahydrofuran-3-yl)-9-benzoylamino-octahydro-10-oxo-6H-

20 **pyridazino[1,2-a][1,2]diazepine-1-carboxamide (245)**, was prepared from (1S,9S) 9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid (**244**), by the method described for **213e**, to afford 601mg (76%) of a colourless foam: IR (KBr) 3401, 2945, 25 1794, 1685, 1638, 1521, 1451, 1120; ¹H NMR (CDCl₃) δ 7.87-7.77 (2H, m), 7.57-7.14 (10H, m), 5.59-5.47 (2H, m), 4.97-4.32 (4H, m), 3.27-1.35 (14H, m); Anal. Calcd for C₂₈H₃₂N₄O₆. 0.5H₂O: C, 63.50; H, 6.28; N, 10.58. Found: C, 63.48; H, 6.14; N, 10.52. MS (ES +, m/z) 30 521 (100%, M⁺ + 1).

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[3S(1*S*,9*S*)] 3-(9-Benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide-4-oxobutanoic acid (**246**), was prepared from [3*S*, 2*RS*(1*S*,9*S*)]N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-9-5 benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**245**), by the method described for **214e**, to afford 396mg (84%) of a white powder: mp. 110-115 °C; $[\alpha]_D^{26}$ -126.3 ° (c 0.2, CH₃OH); IR (KBr) 3345, 2943, 1787, 1730, 1635, 1578, 10 1528, 1488, 1450, 1429; ¹H NMR (CD₃OD) δ 7.88 (2H, m), 7.48 (3H, m), 5.55 (1H, m), 4.91 (1H, m), 4.56 (1H, m), 4.29 (1H, m), 3.41-3.05 (3H, m), 2.76-2.41 (3H, m), 2.28-2.01 (3H, m), 1.86-1.65 (4H, m), 1.36 (1H, m); Anal. Calcd for C₂₁H₂₆N₄O₆. 1.25H₂O: C, 55.68; H, 6.34; 15 N, 12.37. Found: C, 55.68; H, 6.14; N, 12.16. MS (ES -, m/z) 429 (100%, M⁺ - 1).

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[(3*S*(2*R*, 5*S*)]-2,6-Di-tert-butyl-4-methoxyphenyl-3-[5-(2,5-dihydro-3,6-dimethoxy-2-(1-

- 5 **methyl ethyl)pyrazinyl]butanoate (247).** n-Butyllithium (1.6M in hexane) (22.3ml, 35.7mmol) was added dropwise over 20min to a solution of (2*R*)-(-)-2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazine (5.8ml, 6.0g, 32.4mmol) in THF (250ml) cooled to -75 °C at a rate
 10 such that the temperature was maintained below -72 °C. The reaction mixture was stirred for 1h at -75 °C and a solution of 2,6-di-t-butyl-4-methoxyphenyl-2-butenoate (Suzuki et al. Liebigs Ann. Chem. pp. 51-61 (1992))

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(9.9g, 32.5mmol) in THF (60ml) was added over 30 minutes maintaining the temperature below -72 °C during the addition. The reaction mixture was kept at -75 °C for 1.5h and a solution of glacial acetic acid (6ml) in 5 THF (25ml) was added at -75 °C and the solution warmed to room temperature. The solution was poured onto 10% NH₄Cl (300ml) and extracted with diethyl ether (3 x 250ml). The combined organic phases were washed with brine (2 x 200ml), dried over Na₂SO₄ and evaporated to 10 dryness under reduced pressure. The residual oil was purified by flash chromatography on silica gel (20% heptane in CH₂Cl₂) which afforded the title compound as a light yellow oil (13.5g, 85%): [α]_D²⁰ -64 ° (c 0.22, MeOH); IR (KBr) 2962, 2873, 2840, 1757, 1697, 1593, 15 1460, 1433, 1366, 1306, 1269, 1236, 1187, 1157, 1126, 1063, 1038, 1011, 970, 924, 892, 867, 846, 831, 797, 773, 754; ¹H NMR (CDCl₃) δ 6.85 (2H, s), 4.21 (1H, t, J = 3.5), 3.98 (1H, t, J = 3.5), 3.79 (3H, s), 3.71 (3H, s), 3.69 (3H, s), 3.15 (1H, dd, J 17.8, 7.9), 20 2.86-2.81 (1H, m), 2.58 (1H, dd, J = 17.8, 5.9), 2.28- 2.19 (1H, m), 1.33 (18H, s), 1.02 (3H, d, J = 6.8), 0.70 (6H, dd, J = 13, 6.8).

(2S,3S)-5-[2,6-Di-t-butyl-4-methoxyphenyl]1-methyl-3-methylglutamate (248). A solution of [3S(2R, 5S)]-2,6-di-t-butyl-4-methoxyphenyl-3-[5-(2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazinyl)]butanoate (247) (22.4g, 45.8mmol) in acetonitrile (300ml) and 0.25N HCl (366ml, 2 equiv) was stirred at room temperature under nitrogen atmosphere for 4 days. The acetonitrile was 25 evaporated under reduced pressure and diethylether (250ml) was added to the aq. phase. The pH of the aq. phase was adjusted to pH8-9 with concentrated ammonia 30

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solution (32%) and the phases separated. The aq. phase was extracted with diethylether (2 x 250ml). The combined organic phases were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residual oil was purified by flash chromatography on silica gel (2% methanol in CH_2Cl_2) which afforded the required product as a light yellow oil (8.2g, 45%): $[\alpha]_D^{20} +20^\circ$ (*c* 0.26, MeOH); IR (KBr) 3394, 3332, 3000, 2962, 2915, 2877, 2838, 1738, 1697, 1593, 1453, 1430, 1419, 1398, 1367, 1304, 1273, 1251, 1221, 1203, 1183, 1126, 1063, 1025, 996, 932, 891, 866, 847, 800, 772, 745; ^1H NMR (CDCl_3) δ 6.85 (2H, s), 3.79 (3H, s), 3.74 (3H, s), 3.72-3.69 (1H, m), 3.05-2.85 (1H, m), 2.67-2.50 (2H, m), 1.32 (18H, s), 0.93 (3H, d, *J* = 7); Anal. Calcd for $\text{C}_{22}\text{H}_{35}\text{NO}_5$: C, 67.15; H, 8.96; N, 3.56. Found: C, 67.20; H, 9.20; N, 3.70.

(2S,3S)-5-[2,6-Di-t-butyl-4-methoxyphenyl]3-methylglutamate (249). A solution of (2S,3S)-5-[2,6-di-t-butyl-4-methoxyphenyl]3-methylglutamate (248) (8.0g, 20.3mmol) in 5N HCl (200ml) was heated at reflux for 2h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in cyclohexane (x4) and evaporated to dryness (x4) which afforded a white solid (7.9g, 93%): mp 230 $^\circ\text{C}$; $[\alpha]_D^{20} +22^\circ$ (*c* 0.27, MeOH); IR (KBr) 3423, 2964, 1755, 1593, 1514, 1456, 1421, 1371, 1303, 1259, 1201, 1179, 1138, 1106, 1060, 966, 926, 861, 790, 710; ^1H NMR (MeOD) δ 6.76 (2H, s), 4.02 (1H, d, *J* = 3.7), 3.67 (3H, s), 3.05-2.85 (1H, m), 2.80-2.55 (2H, m), 1.22 (18H, s), 1.09 (3H, d, *J* = 6.3); ^{13}C NMR (MeOD) δ 174.5, 171.4, 158.6, 145.2, 143.1, 113.2, 58.3, 56.3, 39.8, 36.9,

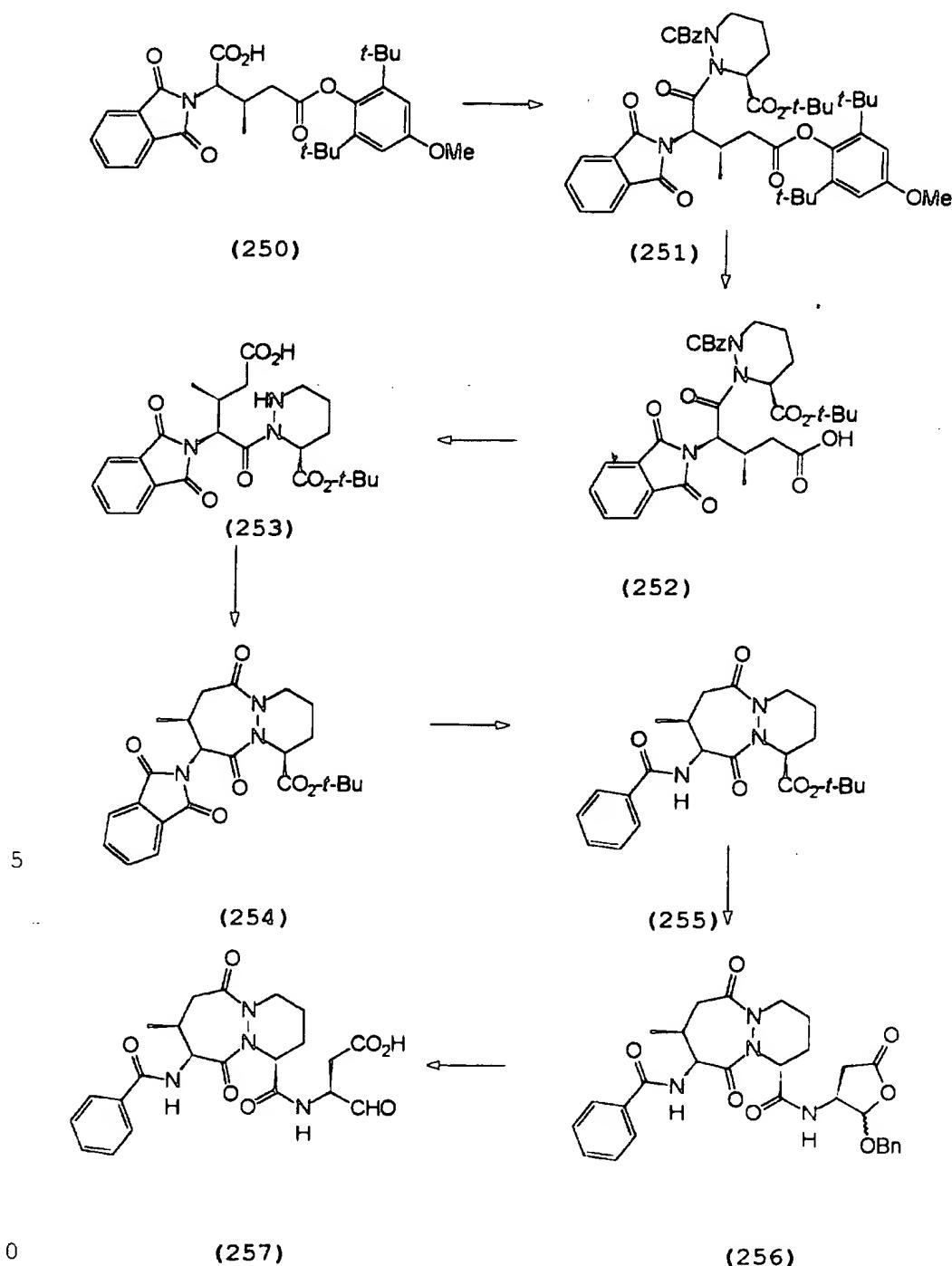
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32.5, 16.6; Anal. Calcd for C₂₁H₃₄ClNO₅: C, 60.64; H, 8.24; N, 3.37. Found: C, 60.80; H, 8.40; N, 3.40.

(2S,3S)-5-[2,6-Di-t-butyl-4-methoxyphenyl]3-methyl-2-phthalimido-1,5-pentanedioate (250),

5 Diisopropylethylamine (4.1ml, 3.04g, 23.5mmol, 1.25 equiv) and phthalic anhydride (3.5g, 23.6mmol, 1.25 equiv) were added to a solution of (2S,3S)-5-[2,6-di-t-butyl-4-methoxyphenyl]3-methylglutamate (249) (7.8g, 18.6mmol) in toluene (300ml). and the resulting mixture
10 was heated at reflux for 3 hours. After cooling to room temperature, the reaction mixture was evaporated to dryness and the resulting oil purified by flash chromatography on silica gel (2% methanol in CH₂Cl₂) which afforded the required product as a white foam
15 (8.35g, 87%): [α]_D²⁰ -20 ° (c 1.04, MeOH); IR (KBr) 3480, 2968, 2880, 1753, 1721, 1594, 1462, 1422, 1388, 1303, 1263, 1216, 1183, 1148, 1062, 1003, 933, 899, 755, 723; ¹H NMR (CDCl₃) δ 7.92-7.87 (2H, m), 7.78-7.73 (2H, m), 6.84 (2H, s), 4.95 (1H, d), 3.78 (3H, s),
20 3.30-3.05 (2H, m), 2.85-2.65 (1H, m), 1.30 (18H, s), 1.13 (3H, d).

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5

10

(257)

(256)

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1-(2,6-di-t-Butyl-4-methoxy)-phenyl-5-(1-benzyloxycarbonyl-3-t-butoxycarbonyl-hexahydro-pyridazin-2-yl)-3-methyl-4-phthalimidopentan-1,5-dioate (251). A solution of the amino acid (250) (1.2g, 5 2.35mmol) in dry diethylether (10ml) was treated with phosphorus pentachloride (0.52g, 2.5mmol) at room temperature for 2h. The mixture was concentrated and treated several times with toluene and again evaporated to dryness. The resulting acid chloride was dissolved 10 in dry THF (5ml) and CH₂Cl₂ (5ml) and cooled to 0 °C. t-Butyl-1-(benzyloxycarbonyl)-hexahydro-3-pyridazine-carboxylate (0.753g, 2.35mmol, 1 equiv) and N-ethylmorpholine (3ml) were added to the solution. The reaction mixture was stirred for 30min at 0 °C and then 15 overnight at room temperature. The mixture was evaporated and the resulting residue taken up with CH₂Cl₂ (30ml). The solution was washed with 1M HCl, water, 10% NaHCO₃, dried (MgSO₄) and evaporated. The resulting white foam was purified on silica gel (0-2% 20 methanol in CH₂Cl₂) which afforded the required compound 251 as a pale yellow glassy solid (740mg, 39%): [α]_D²⁰ -22 (c 0.42, MeOH); IR (KBr) 3441, 2966, 1725, 1693, 1386, 1255, 1221, 1186, 1154, 1123, 1063, 724; ¹H NMR (CDCl₃) δ 7.94-7.89 (4H, m), 7.56-7.28 (5H, m), 6.84 (2H, 2s), 5.29-5.20 (2H, AB), 4.91-4.81 (1H, m), 4.05-3.88 (1H, m), 3.78 (3H, s), 3.75-3.80 (1H, m), 3.28-2.95 (2H, m), 2.23-1.51 (6H, m), 1.45 (9H, s), 1.31 (9H, s), 1.28 (9H, s), 1.27 (3H, d).

(1S, 8S, 9S) t-Butyl 6,10-dioxo-8-methyl-30 1,2,3,4,7,8,9,10-octahydro-9-phthalimido-6H-pyridazino[1,2-a][1,2]diazepin-1-carboxylate (254). A solution of the protected acid (251) (715mg, 0.893mmol)

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in acetonitrile was treated with Cerium (IV) ammonium nitrate (1.8g, 3.3mmol, 3.7 equiv) in water (3ml) for 4h at room temperature. Mannitol (600mg, 3.3mmol, 3.7 equiv) was added and the mixture was stirred for 1h.

- 5 Diethylether (50ml) and water (30ml) were added to the mixture. After decantation, the aq. phase was extracted with diethylether (4 x 50ml). The combined organic phase was washed with water, dried (MgSO_4) and concentrated. Chromatography on silica gel (10% methanol in CH_2Cl_2) afforded 5-(1-benzyloxycarbonyl-3-t-butoxycarbonyl-hexahydropyridazin-2-yl)carbonyl-3-methyl-4-phthalimidopentanoic acid (**252**) (360mg, 64%): $[\alpha]_D^{20} -49.2$ c 0.118, MeOH). This product was used without further purification (360mg, 0.609mmol), and 10 was hydrogenated in methanol (30ml) using 10% Pd/carbon (36mg) for 3h. The reaction mixture was filtered and the resulting solution concentrated to afford the amine (**253**) as a foam (270mg, 96%) $[\alpha]_D^{20} -56.1$ (c 0.18 MeOH). The amine (**253**) was dissolved in dry THF (10ml) and 15 phosphorous pentachloride (305mg, 1.47mmol, 2.5 equiv) was added. The mixture was then cooled to -5 °C and N-ethylmorpholine was added under nitrogen. The reaction mixture was stirred overnight at room temperature. The mixture was concentrated and the residue taken up with 20 CH_2Cl_2 (20ml), cold H_2O (20ml), 1M HCl (20ml). After decantation, the aq. phase was reextracted with CH_2Cl_2 (2 x 20ml). The combined organic phase was washed with 10% NaHCO_3 and water, dried (MgSO_4) and concentrated. The resulting oil was purified on silica gel (1% 25 methanol in CH_2Cl_2) affording the bicyclic compound (**254**) as a solid (65mg, 25%): $[\alpha]_D^{20} -77$ (c 0.208, MeOH); IR (KBr) 3471, 3434, 2975, 2928, 1767, 1723, 1443, 1389, 1284, 1243, 1151, 1112, 720; $^1\text{H NMR}$ (CDCl_3 ,

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δ 7.94-7.69 (4H, m), 5.34-5.27 (1H, m), 4.89-4.66 (2H, m), 3.94-3.64 (2H, m), 3.02-2.84 (1H, m), 2.34-2.19 (2H, m), 1.94-1.61 (3H, m), 1.47 (9H, s), 1.14 (3H, d);
Anal. Calcd for C₂₃H₂₇N₃O₆: C, 62.57; H, 6.17; N, 9.52.
5 Found: C, 62.60; H, 6.40; N, 9.10.

(1*S*, 8*S*, 9*S*) t-Butyl-9-benzoylamino-6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (255). A solution of the bicyclic compound (254) (70mg, 0.16mmol) in
10 ethanol was treated with hydrazine hydrate (0.02ml, 4mmol, 2.5 equiv). After 5h stirring at room temperature, the mixture was concentrated and the resulting residue taken up in toluene and reevaporated. The residue was treated with 2M acetic acid (2ml) for
15 16h. The resulting precipitate was filtered and washed with 2M acetic acid (10ml). The filtrate was basified with solid NaHCO₃ and then extracted with EtOAc. The organic solution was washed with water, dried (MgSO₄) and concentrated. Purification by flash chromatography
20 on silica gel (2% methanol in CH₂Cl₂) afforded the free amine as a foam (50mg, 100%). The amine (50mg, 0.16mmol) was dissolved in dioxane (1ml) and water (0.25ml) and treated with NaHCO₃ (0.034g, 0.04mmol) followed by benzoylchloride (0.047ml, 0.40mmol, 2.8
25 equiv). The mixture was stirred overnight at room temperature, then diluted with EtOAc (15ml). The organic solution was washed with 10% NaHCO₃ and sat. aq. NaCl, dried (MgSO₄) and concentrated. Purification by flash chromatography on silica gel (2% methanol in
30 CH₂Cl₂) afforded the benzamide 255 as a foam (67mg, 100%): ¹H NMR (CDCl₃) δ 7.89-7.39 (5H, m), 6.79 (1H, d), 5.32-5.20 (1H, m), 4.98-4.82 (1H, m), 4.75-4.64

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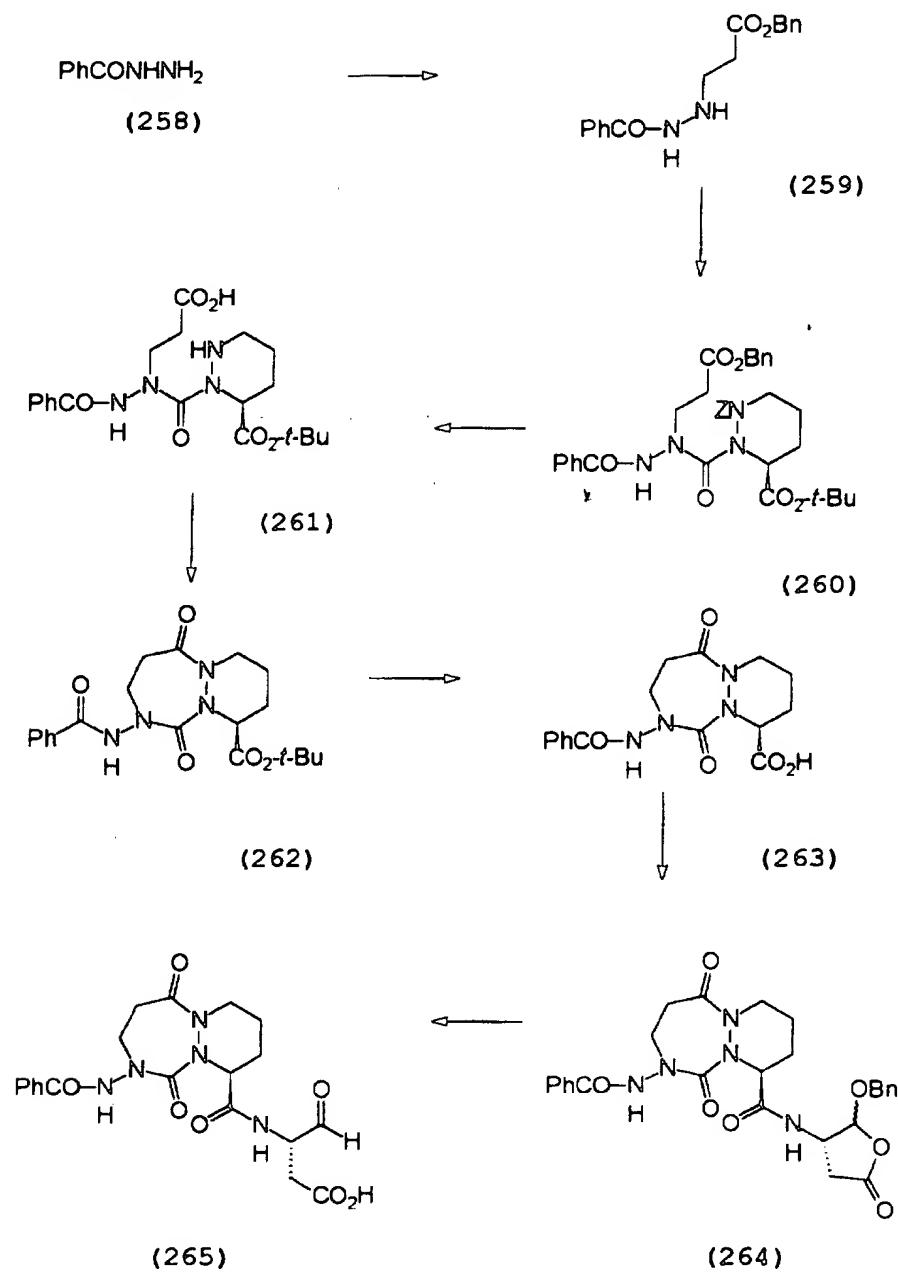
(1H, m), 3.84-3.65 (1H, m), 3.09-2.89 (1H, m), 2.45-
2.18 (2H, m), 2.00-1.61 (4H, m), 1.48 (9H, s), 1.28
(3H, d).

[3S(1S, 8S, 9S)] 3-(9-benzoylamino-6,10-dioxo-8-methyl-
5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid
(257). A solution of t-butyl ester 255 (67mg, 0.16mmol) in CH₂Cl₂ (1ml) was treated at 0 °C with trifluoroacetic acid (1ml). The resulting solution was
10 stirred at 0 °C for 15min and then at room temperature for 1h. The solution was concentrated, the residue taken up in dry CH₂Cl₂ (2 x 2ml) and the mixture again concentrated (x2). The residue was crystallized from diethylether. Filtration of the precipitate afforded
15 the free acid of 255 as a grey solid (40mg, 70%). A solution of acid (40mg, 0.11mmol), N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (Chapman,
Bioorg. & Med. Chem. Lett., 2, pp. 615-18 (1992); 39mg, 0.13mmol, 1.2equiv) and (Ph₃P)₂PdCl₂ (3mg) in a mixture
20 of dry CH₂Cl₂ (1ml) and dry DMF (0.2ml) was treated dropwise with n-Bu₃SnH (0.089ml, 0.33mmol, 3 equiv). The resulting solution was stirred at 25 °C for 10min and then 1-hydroxybenzotriazole (36mg, 0.266mmol, 2.4 equiv) was added. The mixture was cooled to 0 °C and
25 ethyldimethylaminopropyl carbodiimide (31mg, 0.16mmol, 1.5equiv) was added. After stirring at 0 °C for 10min and then at room temperature overnight, the mixture was diluted with EtOAc (20ml) and the resulting solution washed successively with 1M HCl (2 x 5ml), 10% NaHCO₃ (2 x 5ml) and sat. aq. NaCl (5ml), dried (MgSO₄) and concentrated. Flash chromatography on silica gel (2% methanol in CH₂Cl₂) afforded a mixture of

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diastereoisomers (**256**) as a grey solid (50mg, 82%). This product (**256**) was used without further purification (50mg, 0.091mmol) and was hydrogenated in methanol (5ml) using 10% Pd/carbon (30mg) for 24h. The 5 reaction mixture was filtered and the resulting solution concentrated. Flash chromatography on silica gel (2-20% methanol in CH₂Cl₂) afforded compound **257** (9mg, 21%) as a white solid: ¹H NMR (D⁴-MeOH) δ 7.88-7.29 (5H, m), 5.18-4.99 (1H, m), 4.59-4.35 (3H, m), 10 4.26-4.11 (1H, m), 3.65-3.41 (2H, m), 3.18-2.91 (1H, m), 2.62-1.47 (8H, m), 1.29-1.00 (3H, 2d) (mixture of acetal and hemiacetal). MS (ES -) 457.

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Benzyl 3-(N'-benzoylhydrazino)propanoate (259).

Benzylacrylate (1.13ml, 7.34mmol) was added to a
 10 stirred suspension of benzoylhydrazine (285) (1.0g,
 7.34mmol) in isopropanol (28ml). The mixture was

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refluxed for 20h, cooled to room temperature then concentrated. The residue was purified by flash chromatography (20% EtOAc in CH₂Cl₂) to afford 259 (1.098g, 50%) as an oil which crystallized on standing:

5 mp 65 °C; IR (KBr) 3283, 1723, 1644, 1316, 1201, 1156;
1^H NMR (CDCl₃) δ 8.32-8.18 (1H, m), 7.81-7.70 (2H, m),
7.57-7.23 (8H, m), 5.36-4.92 (1H, brm), 5.11 (2H, s),
3.26 (2H, t, J = 6.5), 2.59 (2H, t, J = 6.5); ¹³C NMR
(CDCl₃) δ 172.12, 167.27, 135.65, 132.54, 131.66,
10 128.45, 128.10, 128.06, 126.84, 66.31, 47.33, 33.31;
Anal. Calcd for C₁₇H₁₈N₂O₃: C, 68.44; H, 6.08; N, 9.39.
Found: C, 68.42; H, 6.10; N, 9.38. MS (ES +) 321 (M +
Na, 38%), 299 (M⁺ + 1, 100).

(3S)-1-Benzyl 3-t-butyl 2-(N'-benzoyl-N-(2-

15 **benzyloxycarbonylethyl)hydrazinocarbonyl)hexahydro-**
pyridazine-1,3-dicarboxylate (260). A solution of
(3S)-1-benzyl 3-t-butyl hexahydropyridazine-1,3-
dicarboxylate (Hassall et al. J. Chem. Soc. Perkin 1,
pp. 1451-1454 (1979)) (925.3mg, 2.89mmol) and
20 diisopropylethylamine (0.70ml, 4.0mmol) in a 1.93M
toluene solution of phosgene (17.96ml, 34.7mmol) was
stirred at room temperature for 45min, then
concentrated to leave a yellow solid. To this solid
was added toluene (18ml), hydrazide (259) (861.6mg,
25 2.89mmol) and diisopropylethylamine (0.70ml, 4.0mmol).
The mixture was stirred at room temperature for 2.75h,
then concentrated. The resulting residue was taken up
in EtOAc, washed twice with 1M HCl, brine, then dried
(MgSO₄), filtered and concentrated to afford 2.15g of
30 crude material. Flash chromatography (40% EtOAc in
hexane) afforded 1.65g (89%) of the title compound as a
white foam: mp 40 °C; [α]_D24 -55.78 ° (c 0.40, CH₂Cl₂);

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IR (KBr) 3436, 2930, 1733, 1689, 1455, 1412' 1367, 1258, 1156, 697; ^1H NMR (CDCl_3) δ 8.54-8.23 (0.5H, m), 7.97-7.09 (15.5H), 5.16-4.80 (4H, m), 4.66-4.32 (1H, m), 4.24-3.55 (3.3H, m), 3.50-3.26 (0.4H, m), 3.19-2.49 (2.3H, m), 2.11-1.43 (6H, m), 1.32-1.05 (7H, m); Anal. Calcd for $\text{C}_{35}\text{H}_{40}\text{N}_4\text{O}_8 \cdot 0.5\text{H}_2\text{O}$: C, 64.31; H, 6.32; N, 8.57. Found: C, 64.18; H, 6.27; N, 8.56. MS (ES +) 662 ($\text{M} + \text{Na}$, 84%), 645 ($\text{M}^+ + 1$, 100), 384 (77).

(6S)-3-(N'benzoyl-N-(6-t-butoxycarbonylhexa-

10 **hydropyridazine-1-carbonyl)hydrazino)propanoic acid (261)**. A solution of **260** (1.59g, 2.47mmol) in MeOH (142ml) was treated with 10% Palladium on carbon (230.0mg) and stirred under an atmosphere of H_2 for 1.5h. The mixture was filtered and the solvent 15 evaporated to afford 1.04g (100%) of a white foam. This was used in the next step without further purification: mp <40 °C; $[\alpha]_D^{26} +1.6^\circ$ (c 0.26, CH_2Cl_2); IR (KBr) 3422, 2977, 2986, 1728, 1677, 1486, 1445, 1396, 1369, 1309, 1228, 1155, 916, 716; ^1H NMR 20 (CDCl_3) δ 10.0-9.7 (1H, brm), 7.86 (2H, d, $J = 7.5$), 7.62-7.38 (3H, m), 7.3-5.6 (2H, brm), 4.57 (1H, brd, $J = 4.0$), 4.05-3.77 (2H, m), 3.00-2.82 (1H, m), 2.80-2.43 (3H, m), 2.20-2.03 (1H, m), 2.00-1.47 (1H, m), 1.62-1.14 (11H, m); ^{13}C NMR (CDCl_3) δ 175.00, 171.17, 167.62, 160.68, 132.39, 131.77, 128.67, 127.38, 82.27, 54.38, 48.04, 46.35, 33.62, 28.02, 25.68, 21.61. MS (ES +) 443 ($\text{M} + \text{Na}$, 68%), 421 ($\text{M}^+ + 1$, 100), 365 (50), 131 (61).

(4S)-t-Butyl 7-benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-

30 **octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262)**. To a solution of amino acid **261**

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(1.012g, 2.41mmol) in dry THF (26ml) at 0 °C was added N-ethylmorpholine (597μl, 4.69mmol), followed by PCl₅ (651.3mg, 3.12mmol). The reaction was stirred at 0 °C for 2h, then allowed to warm to rt and stirred for a
5 further 15.5h. The mixture was concentrated and the resulting residue taken up in EtOAc, washed twice with 1M HCl, sat. NaHCO₃, brine, then dried (MgSO₄), filtered and concentrated. Flash chromatography (20% EtOAc in CH₂Cl₂) gave 727.3mg (75%) of the title
10 compound as a white foam: $[\alpha]_D^{26} +51.0^\circ$ (c 0.20, CH₂Cl₂); IR (KBr) 3436, 2979, 1733, 1670, 1483, 1437, 1420, 1299, 1243, 1156; ¹H NMR (CDCl₃) δ 8.70 (1H, s), 7.78 (2H, d, J = 7.0), 7.57-7.32 (3H, m), 5.08 (1H, dd, J = 2.5, 5.5), 4.59-4.43 (1H, m), 4.08-3.69 (3H, m), 15 3.07-2.84 (1H, m), 2.57-2.35 (1H, m), 2.34-2.14 (1H, m), 2.07-1.43 (3H, m), 1.48 (9H, s); ¹³C NMR (CDCl₃) δ 172.41, 169.04, 166.35, 158.35, 132.24, 132.03, 128.61, 127.31, 82.77, 55.41, 54.07, 41.57, 32.21, 28.04, 24.97, 20.37; Anal. Calcd for C₂₀H₂₆N₄O₅: C, 59.69; H, 6.51; N, 13.92. Found: C, 59.53; H, 6.53; N, 13.84.
20 MS (ES +) 425 (M + Na, 71%), 403 (M⁺ + 1, 100), 145 (41).

(4S)-7-Benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-
6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic Acid
25 (263). A solution of ester 262 (720.0mg, 1.80mmol) in a 1:1 mixture of CH₂Cl₂ and TFA (150ml) was stirred for 1.3h under a dry atmosphere. The solution was then reduced *in vacuo*, taken up in Et₂O and reduced again. This process was repeated six times to afford the crude
30 product as an off-white solid. The product was purified by flash chromatography (5% MeOH in CH₂Cl₂) to afford 520.0mg (83%) of the title compound as a white

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foam: $[\alpha]_D^{25} +59.5^\circ$ (c 1.82, CH_2Cl_2); IR (KBr) 3435, 3266, 2956, 1732, 1664, 1524, 1486, 1440, 1302; ^1H NMR (CDCl_3) δ 9.13 (1H, s), 7.77 (2H, d, $J = 7.5$), 7.57-7.32 (3H, m), 5.27-5.16 (1H, m), 4.62-4.43 (1H, m), 5 4.09-2.70 (3H, m), 3.14-2.89 (1H, m), 2.59-2.43 (1H, m), 2.38-2.20 (1H, m), 2.14-1.89 (1H, m), 1.82-1.59 (2H, m); ^{13}C NMR (CDCl_3) δ 173.65, 172.28, 166.44, 158.42, 132.44, 131.31, 128.61, 127.39, 54.83, 54.01, 42.11, 31.79, 24.42, 20.29; MS (ES -) 345 ($M - \text{H}^+$, 10 100%), 161 (45).

[2RS,3S(4S)] N-(2-Benzylxy-5-oxotetrahydrofuran-3-yl)-
6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-
pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264).

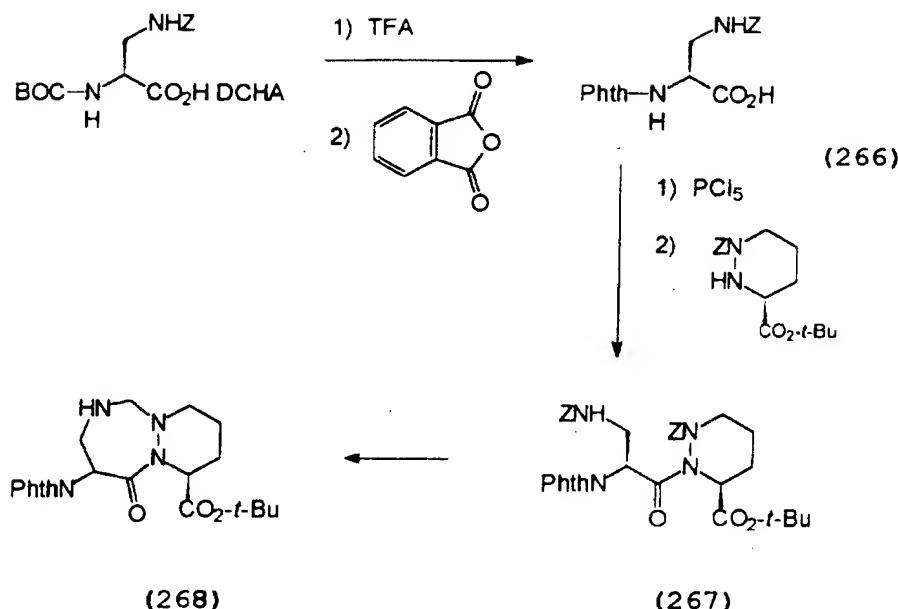
To a solution of acid 263 (300.0mg, 0.87mmol) and
15 (2RS,3S)-3-allyloxycarbonylamino-2-benzylxy-5-
oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett.,
2, pp. 615-18 (1992)) (277.6mg, 0.95mmol) in dry
 CH_2Cl_2 (2.5ml) and dry DMF (2.5ml) at rt was added
bis(triphenylphosphine) palladium chloride (13.0mg),
20 followed by tri-n-butyltin hydride (466.0 μ l, 1.73mmol).
The reaction was stirred for 5min, then 1-
hydroxybenzotriazole (234.1mg, 1.73mmol) was added and
the mixture was cooled to 0 °C before addition of 1-(3-
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
25 (204.5mg, 1.04mmol). The mixture was allowed to warm
to rt and stirred for 16.5h. The mixture was diluted
with EtOAc, washed with 1M NaHSO_4 twice with sat.
 NaHCO_3 , then H_2O and brine. The organic layer was
dried (MgSO_4), filtered and concentrated. The residue
30 was purified by flash chromatography (5% MeOH in
 CH_2Cl_2) to afford 358.3mg (77%) of the title compound
as a white solid: IR (KBr) 3435, 1791, 1665, 1526,

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1421, 1285; ^1H NMR (CDCl_3) δ 8.76 and 8.49 (1H, 2 \times s),
7.92-7.73 (2H, m), 7.62-7.24 (8.5H, m), 6.86 (0.5H, d,
 J = 8.0), 5.53 and 5.33 (1H, d, J = 5.5, s), 4.95-4.34
(5H, m), 4.04-3.54 (3H, m), 3.03-2.64 (2H, m), 2.49-
5 2.14 (2H, m), 2.11-1.46 (4H, m); MS (ES +) 558 (M + Na,
100%), 536 ($M^+ + 1$, 78), 404 (58).

[3S(4S)]3-(7-Benzamido-6,10-dioxo-1,2,3,4,7,8;9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (265). A mixture of
10 264 (350.0mg, 0.65mmol), 10% palladium on carbon
(350mg) and methanol (36ml) was stirred under an
atmosphere of H_2 for 6.5h. The mixture was filtered
and the solvent evaporated. Et_2O was added and the
solvent removed again. This process was repeated four
15 times to reveal 283mg (97%) of the title compound, as a
white crystalline solid: mp decarboxylates above
140 °C; $[\alpha]_D^{26} +33.5^\circ$ (c 0.18, MeOH), IR (KBr) 3428,
1663, 1528, 1487, 1437, 1288; ^1H NMR (D_6 -DMSO) δ 10.56
(1H, s), 8.71-8.57 (1H, m), 7.88-7.81 (2H, m), 7.65-
20 7.46 (3H, m), 4.97-4.85 (1H, m), 4.38-4.0 (3H, m),
3.88-3.52 (3H, m), 2.91-2.71 (2H, m), 2.50-2.38 (1H,
m), 2.35-2.21 (1H, m), 2.10-1.94 (1H, m), 1.93-1.49
(3H, m); ^{13}C NMR (D_6 -DMSO) δ 173.66, 172.49, 169.97,
169.89, 164.96, 157.62, 132.35, 131.85, 128.39, 127.32,
25 53.81, 52.69, 40.90, 33.17, 31.60, 24.40, 24.13, 19.24;
MS (ES -).

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(2S) 3-Benzylxycarbonylamino-2-phthalimidopropionic

- 5 **acid (266).** A solution of (2S) 3-
benzyloxycarbonylamino-2-tert-
butoxycarbonylaminopropionic acid dicyclohexylamine
salt (3g, 5.8mmol) in dichloromethane (200ml) was
washed four times with 1M HCl solution, dried ($MgSO_4$)
10 and concentrated. The resulting oil was dissolved in
dry dichloromethane (35ml), cooled to 0 °C and treated
with trifluoroacetic acid (35ml). This solution was
stirred at 0 °C for 1.5h then evaporated to dryness.
Dichloromethane (50ml) was added to the residue then
15 removed under vacuum. This process repeated six times
to afford a white solid. The white solid was suspended
in toluene (50ml), treated with powdered phthalic
anhydride (940mg, 6.35mmol) and refluxed for 18h. The
resulting solution was concentrated to afford an oil
20 which was purified by flash chromatography (2-10%
methanol/dichloromethane) to afford **266**, 2.01g (94%) as
a white powder: IR (KBr) 3600-2500cm⁻¹, 1776, 1714,

- 435 -

1530, 1469, 1455, 1392, 1263, 1131, 722; ^1H NMR (CDCl_3)
 δ 7.83 (2H, m), 7.72 (2H, m), 7.29 (5H, m), 5.41 (1H,
m), 5.03 (2H, s), 3.90 (2H, m); MS (ES-), 367 (M - 1).

[3S (2S)] t-Butyl 1-benzyloxycarbonyl-2-(3-

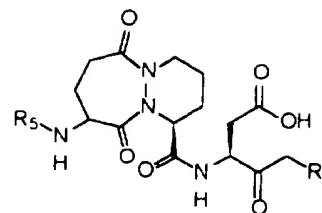
- 5 benzyloxycarbonylamino-2-
phthalimidopropionyl)pyridazine-3-carboxylate (267). A
suspension of the acid 266 (1.32g, 3.58mmol) in dry
ether (37ml) was treated with phosphorus pentachloride
(1.04g, 5mmol) and stirred at room temperature for 2h.
10 The solution was filtered to remove unreacted
phosphorus pentachloride then evaporated to dryness.
The residue was treated with dry toluene (25ml) then
evaporated to dryness. This process was repeated
several times. The resulting oil was dissolved in dry
15 dichloromethane (25ml), cooled to 0 °C and treated with
a solution of (3S) t-butyl 1-
benzyloxycarbonylpyridazine-3-carboxylate (1.15g,
3.58mmol) in dry dichloromethane (2ml) followed by 5%
aqueous sodium bicarbonate solution (25ml). The
20 mixture was stirred rapidly at room temperature for 20h
then diluted with ethyl acetate (100ml) and acidified
to pH2 with 1M HCl. The organic phase was washed twice
with dilute HCl solution then brine, dried (MgSO_4) and
concentrated. The resulting oil was purified by flash
25 chromatography (2-20% ethyl acetate/dichloromethane
then 10-20% methanol/dichloromethane) to afford (267),
1.25g (52%) as a white powder: IR (KBr) 3367, 2955,
1722, 1517, 1455, 1387, 1369, 1251, 1153, 721; ^1H NMR
(CDCl_3) δ 7.81 (2H, m), 7.74 (2H, m), 7.63 (1H, brs),
30 7.31 (10H, m), 5.46-4.76 (5H, m), 4.07-3.54 (4H, m),
2.4 (1H, m), 2.0-1.6 (3H, m), 1.40 (9H, s); MS (ES+),
671 (M + 1), 693 (M + Na).

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(1*S*,9*S*) *t*-Butyl 1,2,3,4,7,8,9,10-octahydro-10-oxo-9-phthalimido-6*H*-pyridazino[1,2-*a*][1,2,4]triazepine-1-carboxylate (**268**). A solution of ester **267** (50mg, 0.074mmol) in methanol (15ml) was treated with 10% palladium on carbon (50mg) and hydrogenated at room temperature and atmospheric pressure for 24h. The mixture was evacuated thoroughly to remove hydrogen then treated with 37% aqueous formaldehyde (18mg, 0.22mmol) and stirred under nitrogen for 2h. The mixture was filtered, evaporated to dryness and the product purified by flash chromatography (4-100% ethyl acetate/dichloromethane) to afford **268** 14.5mg (48%) as an oil: ^1H NMR (CDCl_3) δ 7.85 (2H, m), 7.71 (2H, m), 5.78 (1H, dd, J = 10, 5), 4.99 (1H, dd, J = 6.1, 1.5), 4.07 (1H, d, J = 10.6), 3.49 (1H, dd, J = 14, 5), 3.39 (1H, d, J = 10.3), 3.24 (1H, dd, J = 14, 10.2), 3.17 (2H, m), 2.39 (1H, m), 1.84-1.46 (3H), 1.51 (9H, s); MS (ES+), 415 ($M + 1$), 437 ($M + \text{Na}$).

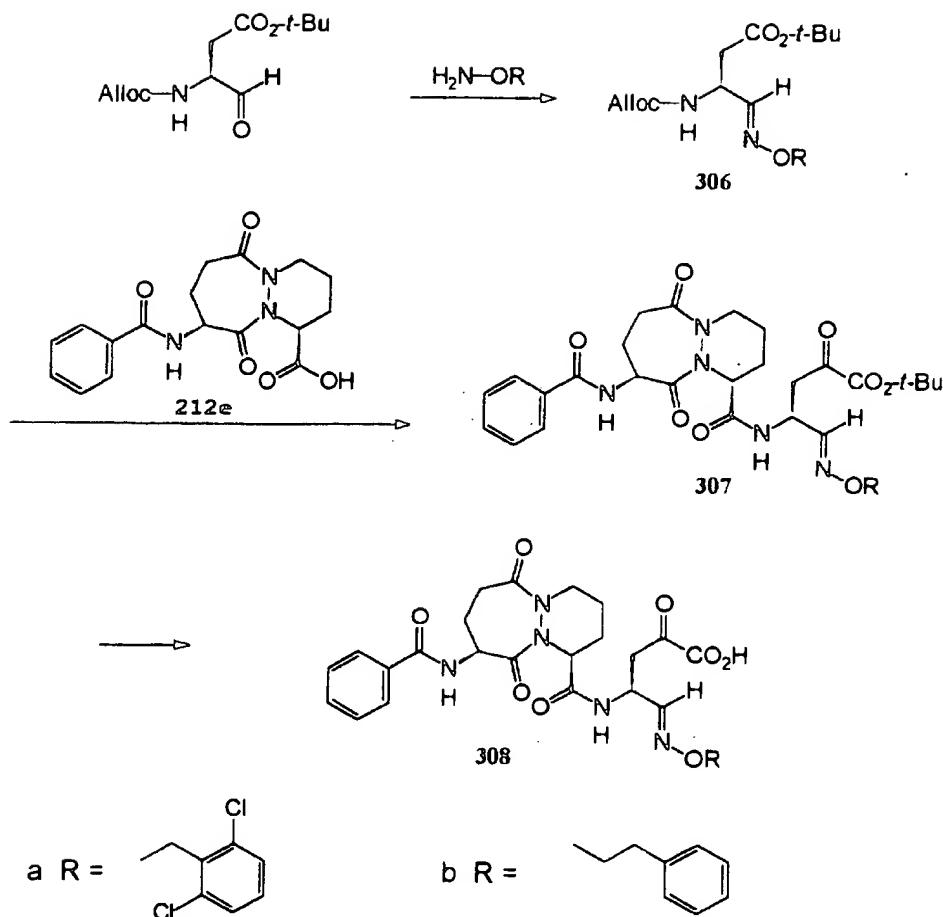
Compounds **280-283** were prepared from **212b** by a method similar to the method used to prepare **226e**. Compounds **284-287** were prepared by a method similar to the method used to prepare **217e**.

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**280-287**

compound	R ₅	R
280		
281		
282		
283		
284		
285		
286		
287		

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(3S) 3-Allyloxycarbonylamino-4-oxobutyric acid tert-butyl ester O-(2,6-dichlorophenylmethyl)oxime (306a) was prepared by a similar procedure as 208a except that 2,6-dichlorophenylmethoxyamine (prepared by a similar method as 306b) was used instead of semicarbazide to give 870mg (quant.) as a clear oil.

(3S) 3-Allyloxycarbonylamino-4-oxobutyric acid tert-butyl ester O-(2-(phenyl)ethyl)oxime (306b) was prepared by a similar procedure as 208a except that 2-

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(phenyl)ethoxyamine (US 5 346 911) was used instead of semicarbazide to give 395mg (quant.) as a clear oil.

[3S(1S,9S) 3-(9-Benzoylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

5 [1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-
oxobutanoic acid t-butyl ester, O-(2,6-
dichlorophenylmethyl)oxime (307a) was prepared by a
procedure similar to 233e except 306a was used instead
of 207a to give 23 mg(23%) of 307a as a white solid.

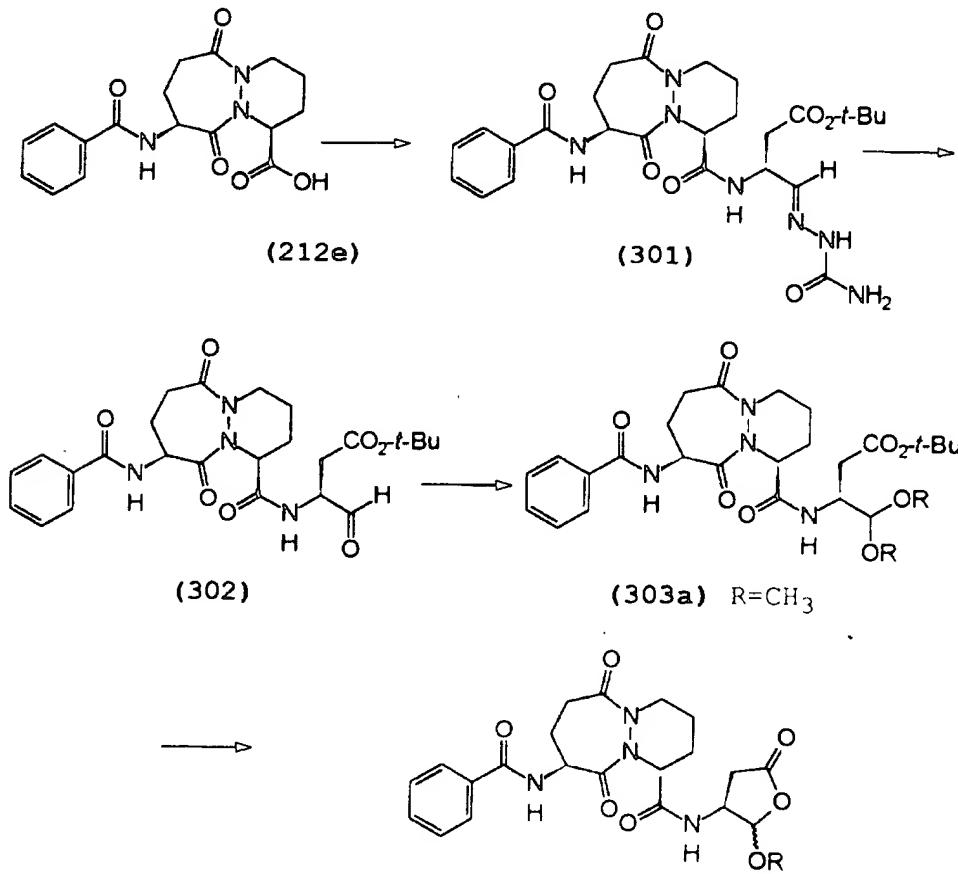
10 [3S(1S,9S) 3-(9-Benzoylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-
oxobutanoic acid t-butyl ester, O-(2-
<phenyl>ethyl)oxime (307b) was prepared by a procedure
15 similar to 233e except 306b was used instead of 207a to
give 43 mg(48%) of 307b as a white solid.

[3S(1S,9S) 3-(9-Benzoylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-

20 oxobutanoic acid, O-(2,6-dichlorophenylmethyl)oxime
(308a) was prepared by from 307a a procedure similar to
the preparation of 235e from 234e to give 15.2 mg (74%)
as white solid: ^1H NMR(CD₃OD) δ 0.9(m), 1.3(s),
1.7(m), 1.8(m), 2.0(m), 2.1-2.2(m), 2.3(dd), 2.4-
2.5(m), 2.6(m), 2.7-2.8(m), 3.1(m), 3.3(m), 3.4-3.5(m),
4.5(m), 4.9(m), 5.1(m), 5.3(d), 5.4(s), 6.8(d), 7.2-
7.5(m), 7.8(dd), 8.4(dd).

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[3S(1S,9S) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid, O-(2-(phenyl)ethyl)oxime (308b) was prepared by from 307b a procedure similar to the preparation of 235e from 234e to give 25.2 mg (68%) as white solid: ^1H NMR (CD_3OD) δ 1.2(m), 1.6-1.7(m), 2.0-2.1(m), 2.2(m), 2.3(m), 2.5(m), 2.6-2.7(dd), 2.9(t), 3.0(t), 3.1(m), 3.3-3.5(m), 4.2(t), 4.25(m), 4.5(m), 5.2(t), 5.3(t), 6.7(d), 7.1-7.2(m), 7.35(dd), 7.4(m), 7.5(m), 7.8(dd), 8.3(dd).



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[3S(1S,9S) 3-(9-Benzoylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-
oxobutanoic acid tert-butyl ester (302).

- 5 **Step A:** 301 was prepared by procedure similar to 605a
(Step A), except 212e was used instead of 603a to give
540 mg (34%) to give a white solid.
- Step B: 302. A solution of 301 (50.7 mg; 0.091 mmol)
in 2.8 ml of MeOH/HOAc/37% aq. formaldehyde (5:1:1) was
10 stirred at rt for 5.5 h. and the reaction was
concentrated to 0.7 ml *in vacuo*. The residue was
dissolved in 3 ml of CH₃CN and concentrated to 0.7 ml
(3x), dissolved in toluene and concentrated to 0.7 ml
in vacuo (2x), and concentrated to dryness.
- 15 Chromatography (flash, SiO₂, 5% isopropanol/CH₂Cl₂) gave
302 (45.5 mg, 78%) as a white solid: ¹H NMR(DMSO-d₆) δ
1.0-1.15(m, 2H), 1.4(s, 9H), 1.65(m, 2H), 1.9-2.1(m,
2H), 2.15-2.4(m, 3H), 2.55(m, 1H), 2.7-3.0(m, 2H), 4.3-
4.6(m, 2H), 4.9(m, 1H), 5.2(m, 1H), 7.4-7.6(m, 2H),
20 7.8-8.0(m, 2H), 8.6(m, 1H), 8.8(m, 1H), 9.4(s, 1H).

[1S,9S (2RS,3S)] 9-Benzoylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-N-(2-methoxy-5-oxo-
tetrahydro-furan-3-yl)-6H-pyridazino[1,2-a][1,2]
diazapine-1-carboxamide. (304a).

- 25 **Step A:** A solution of 302 (90 mg; 0.18 mmol) in 10 ml
of MeOH was treated with trimethylorthoformate (1ml)
and p-toluene sulfonic acid hydrate (5 mg; 0.026 mmol)
and the reaction was stirred for 20 h. The reaction
was treated with 3 ml of aq. sat. NaHCO₃ and
30 concentrated *in vacuo*. The residue was taken up in

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EtOAc and washed with dilute aq. NaHCO₃, dried over MgSO₄ and concentrated *in vacuo* to give 80 mg of **303a**.

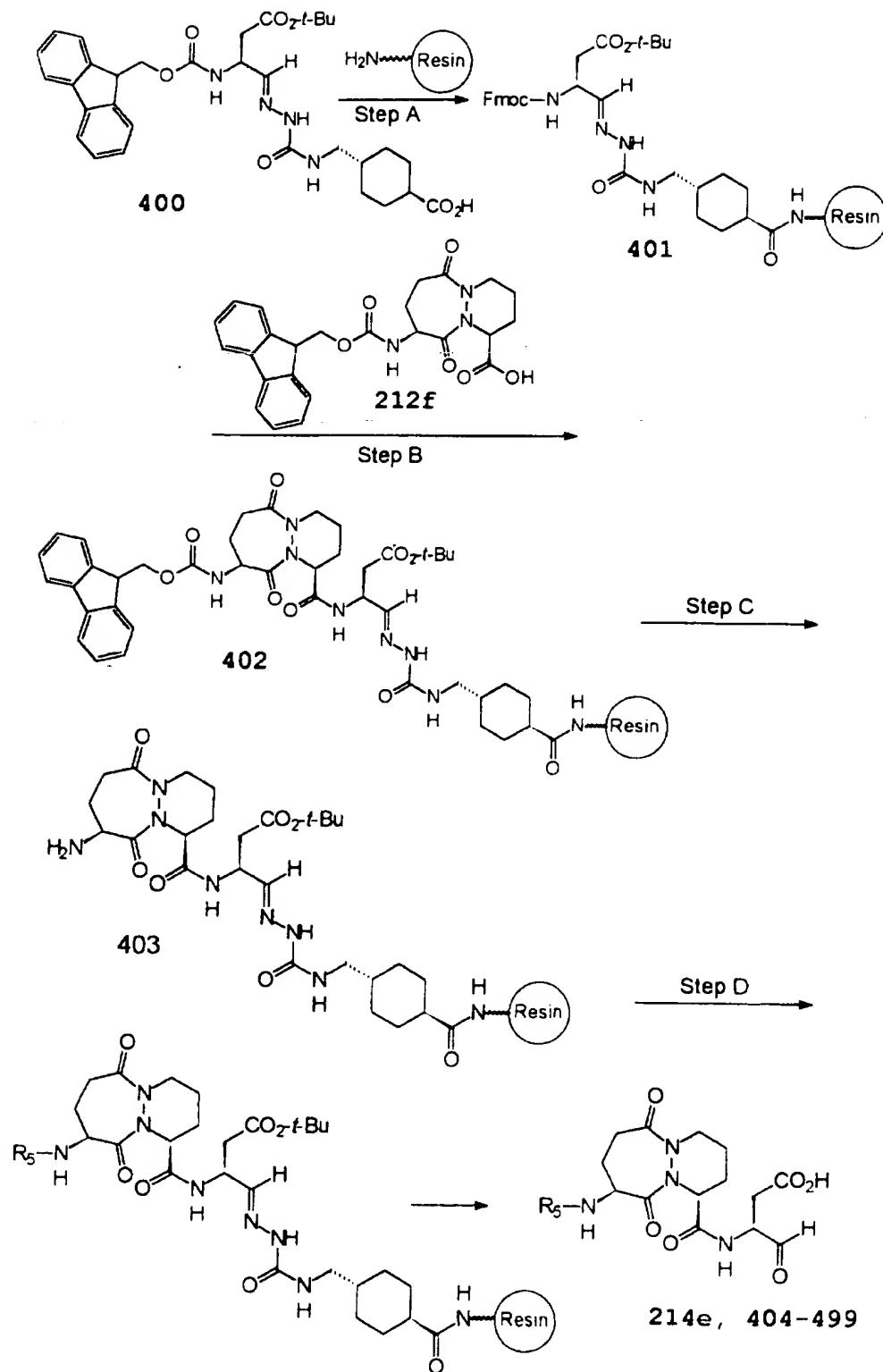
Step B: **303a** was dissolved in 2 ml of TFA and stirred at rt for 15 min. The reaction was dissolved in CH₂Cl₂

5 and concentrated *in vacuo* (3x). Chromatography (flash, SiO₂, 1% to 3% MeOH/CH₂Cl₂ gave 43 mg (64%) of **304a** as a white solid: ¹H NMR(CDCl₃) δ 1.55-1.8(m, 2H), 1.9-2.15(m, 4H), 2.25-2.5(m, 2H), 2.7-3.3(m, 4H), 3.45, 3.6(s, s, 3H), 4.4, 4.75(2m, 1H), 4.6(m, 1H), 4.95, 10 5.4(t,d, 1H), 5.1-5.2(m, 1H), 6.45, 7.05(2d, 1H), 6.95(m, 1H), 7.45(m, 2H), 7.5(m, 1H), 7.85(m, 2H).

Example 11

Compounds **214e**, **404-413**, **415-445**, **446-468**,
470-491, and **493-499** were synthesized as described in
15 Example 11 and Table 7.

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Step A. Synthesis of 401. TentaGel S[®] NH₂ resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with DMF (3 x 50 mL), 10% (v/v) DIEA in DMF (2 x 50 mL) and finally with DMF (4 x 50 mL).

- 5 Sufficient DMF was added to the resin to obtain a slurry followed by 400 (1.42 g, 2.4 mmol, prepared from (3*S*)-3-(fluorenethylmethyloxycarbonyl)-4-oxobutyric acid *t*-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-
- 10 hydroxybenzotriazole hydrate (HOBT·H₂O; 0.367 g, 2.4 mmol), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU; 0.91 g, 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin
- 15 was isolated on a sintered glass funnel by suction filtration and washed with DMF (3 x 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) Ac₂O/DMF (2 x 25 mL) directly in the funnel (10 min/wash). The resin was washed with DMF (3
- 20 x 50 mL) and CH₂Cl₂ (3 x 50 mL) prior to drying overnight *in vacuo* to yield 401 (11.0 g, quantitative yield).

- Step B. Synthesis of 402.** Resin 401 (6.0 g, 0.16 mmol/g, 0.96 mmol) was swelled in a sintered glass
- 25 funnel by washing with DMF (3 x 25 mL). The Fmoc protecting group was then cleaved with 25% (v/v) piperidine/DMF (25 mL) for 10 min (intermittent stirring) and then for 20 min with fresh piperidine reagent (25 mL). The resin was then washed with DMF (3
- 30 x 25 mL), followed by N-methylpyrrolidone (2 x 25 mL). After transferring the resin to a 100 mL flask, N-methylpyrrolidone was added to obtain a slurry followed

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by **212f** (0.725 g, 1.57 mmol), HOBT·H₂O (0.25 g, 1.6 mmol), HBTU (0.61 g, 1.6 mmol) and DIEA (0.84 mL, 4.8 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin work-up and 5 capping with 20% (v/v) Ac₂O in DMF were performed as described for **401** to yield **402** (6.21 g, quantitative yield).

Step C. Synthesis of 403. This compound was prepared from resin **402** (0.24 g, 0.038 mmol) using an 10 Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with DMF (3 x 1 mL), deprotection with 25% (v/v) piperidine in DMF (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **403**. The resin was washed 15 with DMF (3 x 1 mL) and *N*-methylpyrrolidone (3 x 1 mL).

Step D. Method 1. [3*S*(1*S*,9*S*)]-3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(thiophene-3-carbonylamino)-6*H*-pyridazine[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (**409**). Resin **403** was 20 acylated with a solution of 0.4M thiophene-3-carboxylic acid and 0.4M HOBT in *N*-methylpyrrolidone (1 mL), a solution of 0.4M HBTU in *N*-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in *N*-methylpyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at rt. The 25 acylation step was repeated. Finally, the resin was washed with DMF (3 x 1 mL), CH₂Cl₂ (3 x 1 mL) and dried *in vacuo*. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/5% H₂O (v/v, 1.5 mL) for 30 min at rt. After washing the 30 resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 Et₂O:pentane (12 mL)

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and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% CH₃CN/90% H₂O/0.1% TFA (15 mL) and lyophilized to obtain crude **409** as a white powder. The 5 compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 x 250 mm) eluting with a linear CH₃CN gradient (5% - 45%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were pooled 10 and lyophilized to provide **409** (10.8 mg, 63%).

Step D. Method 1A. Synthesis of 418. Following a similar procedure as method 1, resin **403** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described 15 in Step C and the free amine was acetylated with 20% (v/v) Ac₂O in DMF (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2 hr at rt. The acetylation step was repeated. Cleavage of the aldehyde from the resin gave **418** (3.2 mg).

20 **Step D. Method 1B. Synthesis of 447.** Following a similar procedure as method 1A, resin **403** was acylated with 0.4M 4-(1-fluorenylmethoxycarbonylamino)benzoic acid. The acylation step was repeated once. The Fmoc group was 25 removed as before and the free amine was reacted with 1M methanesulfonyl chloride in CH₂Cl₂ (0.5 mL) and 1M pyridine in CH₂Cl₂ (0.60 mL) for 4 hr at rt. Cleavage of the aldehyde from the resin gave **447** (10.0 mg).

30 **Step D. Method 2. Synthesis of 214e.** Following a similar procedure as method 1, resin **403** was acylated

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with 0.5M benzoyl chloride in *N*-methylpyrrolidone (1 mL) and 1.6M DIEA in *N*-methylpyrrolidone (0.35 mL) for 2 hr at rt. The acylation step was repeated. Cleavage of the aldehyde from the resin gave 214e (5.1 mg, 30%).

5 **Step D. Method 3. Synthesis of 427.** Following a similar procedure as method 1, resin 403 was reacted with 1.0M benzenesulfonyl chloride in CH₂Cl₂ (0.5 mL) and 1M pyridine in CH₂Cl₂ (0.60 mL) for 4 hr at rt. The reaction was repeated. Cleavage of the aldehyde
10 from the resin gave 427 (7.2 mg, 40%).

Step D. Method 4. Synthesis of 420. Following a similar procedure as method 1, resin 403 was reacted with 0.5M methylisocyanate in *N*-methylpyrrolidone (1 mL) and 1.6M DIEA in *N*-methylpyrrolidone (0.35 mL) for 2
15 hr at rt. The reaction was repeated. Cleavage of the aldehyde from the resin gave 420 (8.3 mg, 55%).

Step D. Method 5. Synthesis of 445. Following a similar procedure at method 1, resin 403 was acylated with 0.27M imidazole-2-carboxylic acid (1 mL) in 2:1
20 DMF:H₂O (with 1 eq. DIEA) and 1M 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in 2:1 *N*-methylpyrrolidone/H₂O (0.35 mL) for 3 hr at rt. Cleavage of the aldehyde from the resin gave 445 (9.5 mg).

25 Analytical HPLC methods:

(1) Waters DeltaPak C18, 300A (5 μ , 3.9 x 150 mm., Linear CH₃CN gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

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(2) Waters DeltaPak C18, 300A (5 μ , 3.9 x 150 mm).

Linear CH₃CN gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

(3) Waters DeltaPak C18, 300A (5 μ , 3.9 x 150 mm).

5 Isocratic elution with 0.1% TFA/water (v/v) at 1 mL/min.

(4) Waters DeltaPak C18, 300A (5 μ , 3.9 x 150 mm).

Linear CH₃CN gradient (0% - 30%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

10 (5) Waters DeltaPak C18, 300A (5 μ , 3.9 x 150 mm).

Linear CH₃CN gradient (0% - 35%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

Table 7

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
214e		C21H24N4O7	444.45	6.67 (2) 98%	445	2
404		C22H26N4O7	458.48	6.66 (2) 97%	459	2
405		C22H26N4O8	474.47	8.2 (1) 98%	475	2

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Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
406		C21H23ClN4O7	478.89	6.33 (1) 98%	479	2
407		C25H26N4O7	494.51	9.90 (1) 98%	495	2
408		C25H26N4O7	494.51	9.0 (1) 98%	495	2
409		C27H28N4O7	520.55	11.14 (1) 98%	521	2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
410		C19H22N4O7S	450.47	4.87 (1) 98%	451	1
411		C24H25N5O7	495.50	10.7 (1) 98%	496	1
412		C24H25N5O7	495.50	8.57 (1) 98%	496	1
413		C18H24N4O7	408.41	7.21 (2) 98%	409	1

Cmpd.	Structure	MF	MW	HPLC min	RT	MS (M+H) +	Syn. Method
415		C22H24N4O9	488.46	7.58 (1) 98%	489	1	
416		C21H23ClN4O7	478.89	9.66 (1) 98%	479	1	
417		C24H30N4O10	534.53	8.12 (1) 535	535	1	

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
418		C23H27N5O8	501.50	5.93 (1) 98%	502	1A
419		C16H22N4O8	398.38	6.84 (2) 98%	399	2
420		C16H23N5O7	397.39	5.25 (2) 98%	398	4

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
421		C16H24N4O8S	432.46	7.13 (2) 98%	433	3
422		C21H28N6O7	476.49	6.89 (1) 98%	477	1
423		C20H25N5O7S	479.52	5.62 (1) 98%	480	1
424		C19H23N5O8	449.42	6.28 (1) 450	450	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
425		C25H26N4O8	510.51	8.25 (1) 98%	511	1
426		C21H30N4O7	450.50	8.0 (1) 98%	451	2
427		C20H24N4O8S	480.50	7.87 (1) 98%	481	3

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
428		C16H25N5O8S	447.47	5.13 (1) 98%	448	3
429		C14H20N4O6	340.34	3.19 (3) 98%	341	
430		C23H27N5O8	501.50	5.53 (1) 98%	502	1A
431		C21H25N5O7	459.46	6.66 (2) 98%	460	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
432		C21H23N7O7	485.46	5.59 (1) 98%	486	1
433		C24H27N5O7	497.51	11.07 (1) 97%	498	1
434		C22H24N6O7	484.47	4.43 (1) 98%	485	1
435		C24H25N5O7	495.50	5.10 (1) 98%	496	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
436		C24H25N5O7	495.50	8.20 (4) 98%	496	1
437		C25H27N5O8	525.52	12.78 (5) 98%	526	1
438		C24H25N5O7	495.50	4.85 (1) 98%	496	1
439		C24H25N5O7	495.50	8.70 (5) 98%	496	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
440		C25H27N5O7	509.52	9.96 (5) 98%	510	1
441		C27H31N5O7	537.58	6.15 (1) 98%	538	1
442		C21H22N4O7S2	506.56	10.10 (1) 98%	507	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
443		C27H28N4O8	536.55	13.12 (1) 98%	537	1
444		C21H22Cl2N4O7	513.34	9.96 (5) 98%	510	1
445		C18H22N6O7	434.41	5.72 (1) 98%	435	5

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
446		C17H20N6O7S	452.45	5.00 (1) 98%	453	1
447		C22H27N5O9S	537.55	6.32 (1) 98%	538	1B
448		C24H29N5O8	515.53	6.36 (1) 98%	516	1A

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
449		C25H26N4O8	510.51	13.86 (1) 98%	511	1
450		C23H27N5O8	501.50	6.10 (1) 98%	502	1A
451		C22H26N4O8	474.47	8.02 (1) 98%	475	2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
452		C22H26N4O8	474.47	7.77 (1) 98%	475	2
453		C23H24N4O7S	500.53	11.11 (1) 98%	501	2
454		C20H23N5O7	445.44	6.24 (2) 98%	446	2
455		C21H23C1N4O7	478.89	9.45 (1) 98%	479	2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
456		C21H24N4O8	460.45	5.58 (1) 98%	(M+Na) 483	1
457		C28H28N4O10	580.56	10.42 (1) 98%	(M+Na) 603	1
458		C21H22F2N4O7	480.43	8.65 (1) 98%	481.1	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
459		C21H22ClFN4O7	496.88	10.11 (1) 98%	498.3	1
460		C22H26N4O9S	522.54	6.16 (1) 98%	523.6	1
461		C21H23FN4O7	462.44	7.41 (1) 98%	463.3	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
462		C21H23FN4O7	462.44	7.71 (1) 98%	463.3	1
463		C21H23FN4O7	462.44	7.64 (1) 98%	464	1
464		C21H22Cl2N4O7	513.34	11.59 (1) 98%	414.5	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
465		C22H25ClN4O7	492.92	9.65 (1) 98%	493.9	1
466		C22H25ClN4O7	492.92	9.63 (1) 98%	493.9	1
467		C23H24N4O8	484.47	9.73 (1) 98%	485.8	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
468		C26H26F3N5O7S	609.59	14.84 (1) 98%	609.7	1
470		C23H29N5O7	487.52	4.57 (1) 98%	489.5	1
471		C23H29N5O7	487.52	5.74 (1) 98%	488.2	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
472		C22H25N5O7	471.47	4.00 (1) 98%	474	1
473		C23H26N4O9	502.49	7.65 (1) 98%	503.6	1
474		C23H26N4O8	486.49	7.16 (1) 98%	488.1	1

Cmpd.	Structure	MF	MW	HPLC min	MS (M+H) +	Syn. Method
475		C23H25N5O7	483.49	9.77 (1) 97%	485.1	1
476		C22H26N4O8	474.47	5.25 (1) 98%	475.8	1
477		C26H33N5O9	559.58	4.76 (1) 95%	561.8	1

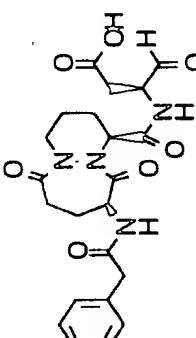
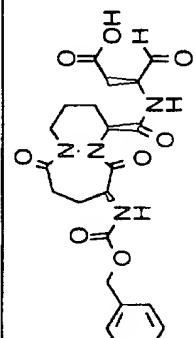
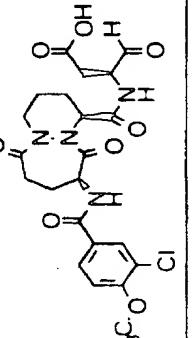
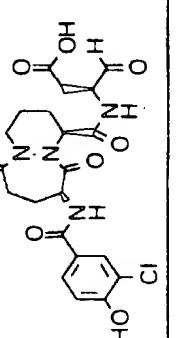
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
478		C21H25N5O9S	523.53	5.25 (1) 98%	524.3	1
479		C22H26N4O8	474.47	5.35 (1) 98%	475.8	1
480		C25H30N6O9	558.55	5.11 (1) 98%	559.3	1A

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
481		C21H24ClN5O7	493.9	7.10 (1) 98%	495.1	1
482		C21H23Cl2N5O7	528.4	9.05 (1) 98%	529.8	1
483		C28H29N5O8	563.57	10.01 (1) 98%	565.6	1,2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
484		C25H31N5O8	529.55	7.88 (1) 98%	531	1,2
485		C24H29N5O8	515.53	7.00 (1) 98%	517.6	1,2
486		C29H31N5O8	577.60	10.43 (1) 98%	579.4	1,2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
487		C26H33N5O8	543.58	9.30 (1) 98%	545.7	1,2
488		C25H31N5O8	529.55	8.13 (1) 98%	531.1	1,2
489		C23H28N6O8	516.52	5.89 (1) 98%	517.8	1,4
490		C23H27N5O9	517.50	7.27 (1) 98%	(M+Na) 540.8	1,2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
491		C28H28N4O9	564.56	12.9 (1) 98%	565.3	1
493		C22H25FN4O8	492.46	8.31 (1) 98%	493.9	1
494		C23H26N4O7	470.49	9.34 (1) 98%	471.2	2

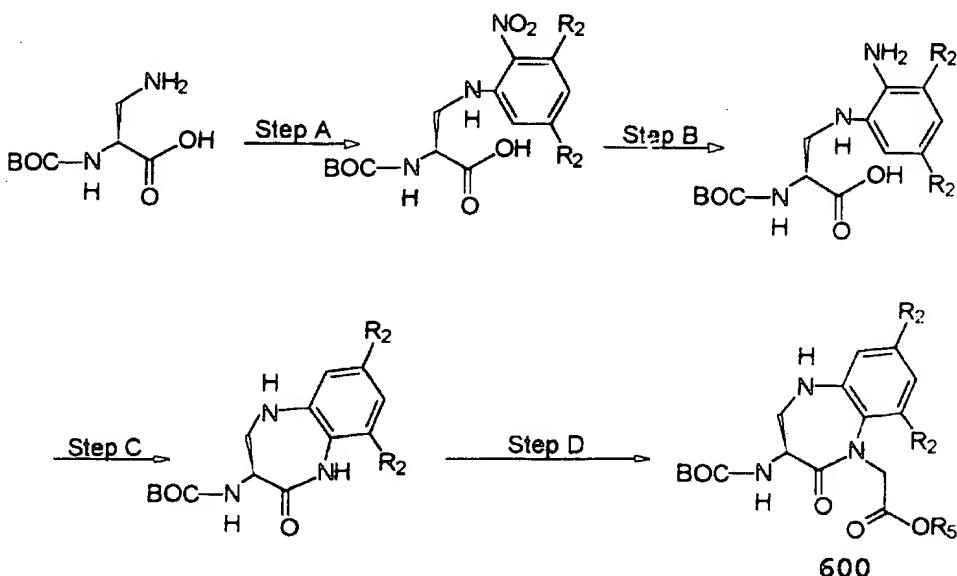
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
495		C22H26N4O7	458.48	7.24 (1) 98%	459.9	2
496		C22H26N4O8	474.47	9.47 (1) 98%	475.7	2
497		C22H25ClN4O8	508.92	9.58 (1) 98%	509.5	1
498		C21H23ClN4O8	494.89	7.18 (1) 98%	495.1	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
499		C ₂₈ H ₃₀ N ₄ O ₈	550.57	13.27 (1) 98%	552	1

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Example 12

Compounds 605a-j, 605m-q, 605s, 605t, and 605v were synthesized as described below.



Compound no.	R ₂	R ₅
5 600a/103	H	CH ₃
600b	H	CH ₂ Ph
600c	CH ₃	CH ₂ Ph

(3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103).

Step A. (2S)-2-tert-Butoxycarbonylamino-3-(2-nitrophenyl-amino)-propionic acid. (2S)-2-tert-Butoxycarbonylamino-3-aminopropionic acid (10 g, 49 mmol), 2-fluoronitrobenzene (5.7 ml, 54 mmol), and 15 NaHCO₃ (8.25 g, 98 mmol) was taken into 130 ml of DMF

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and heated at 80 °C for 18 h. The reaction was evaporated *in vacuo* to give a viscous orange residue that was dissolved in 300 ml of H₂O and extracted with Et₂O (3 x 150 ml). The aq. solution was acidified to pH 5 with 10% NaHSO₄ and extracted with EtOAc (3 x 250 ml). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and evaporated to give 12.64 g (83%) of the title compound as an orange amorphous solid: ¹H NMR (CD₃OD) δ 8.15-8.10 (1H, d), 7.54-7.48 (1H, t), 7.13-10 7.08 (1H, d), 6.73-6.65 (1H, t), 4.45-4.35 (1H, m), 3.9-3.8 (1H, dd), 3.65-3.55 (1H, dd), 1.45 (9H, s).

Step B. (2S)-2-tert-Butoxycarbonylamino-3-(2-aminophenyl-amino)-propionic acid. A mixture of (2S)-2-tert-Butoxycarbonylamino-3-(2-nitrophenylamino)propionic acid (12.65 g, 40.5 mmol) and 0.5 g of 10% Pd/C in 100 ml of MeOH under hydrogen at 1 atmosphere was stirred for 4 h. The solution was filtered through Celite 545 and the filtrate evaporated *in vacuo* to afford the 11.95 g of the title compound in quantitative yield as a dark brown solid that was used without purification: ¹H NMR (CD₃OD) δ 6.75-6.70 (3H, m), 6.65-6.58 (1H, m), 4.35-4.3 (1H, m), 3.6-3.38 (2H, m), 1.45 (9H, s).

Step C. (3S)-2-Oxo-3-tert-Butoxycarbonylamino-1,3,4,5-tetrahydro-1H-1,5-benzodiazepine. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.54 g, 44.5 mmol) was added to a cooled (0 °C) solution of (2S)-2-tert-butoxycarbonylamino-3-(2-aminophenylamino)propionic acid (11.95 g, 40.5 mmol) in 100 ml of DMF and stirred for 18 h. The reaction was poured into 700 ml of EtOAc and washed four times with

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100 ml of H₂O. The organic layer was dried over anhydrous Na₂SO₄, filtered, and evaporated to give a brown solid that was purified by flash chromatography eluting with 3:7 EtOAc/hexane to give 8 g (71%) of the title compound: ¹H NMR (CDCl₃) δ 7.78 (1H, s), 7.02-6.95 (1H, m), 6.88-6.82 (1H, m), 6.82-6.78 (1H, m), 6.75-6.70 (1H, m), 5.8-5.7 (1H, d), 4.55-4.45 (1H, m), 3.95 (1H, s), 3.9-3.82 (1H, m); 3.48-3.40 (1H, m), 1.45 (9H, s).

10 **Step D. (3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103).** A 1.0 M solution of lithium bis(trimethylsilyl)amide (3.4 ml, 3.4 mmol) in THF was added dropwise to a -78 °C solution of (3S)-2-oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (0.94 g, 3.38 mmol) in 20 ml of anhydrous THF and stirred for 30 min. Methyl bromoacetate (0.44 ml, 4 mmol) was added dropwise to the reaction mixture then warmed to RT. The reaction was diluted with 100 ml of EtOAc and washed with 0.3N KHSO₄ (50 ml), H₂O (2 × 50 ml), and brine. The combined organics were dried over anhydrous Na₂SO₄, filtered, and evaporated to afford a gum that was purified by flash chromatography eluting with 3:7 EtOAc/Hex. to give 0.98 g (83%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.15-7.07 (2H, m), 6.98-6.94 (1H, m), 6.88-6.84 (1H, d), 5.62-5.55 (1H, d), 4.71-4.65 (1H, d), 4.65-4.6 (1H, m), 4.33-4.27 (1H, d), 3.96-3.90 (1H, m), 3.78 (3H, s), 3.44-3.37 (1H, m), 1.4 (9H, s).

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(3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600b). Prepared by a similar method described for the preparation of 600a/103 (Step D), except benzyl bromoacetate was used instead of methyl bromoacetate to give 600b in quantitative yield.

(3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600c).

10 Step A. (2S)-2-tert-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenylamino)-propionic acid. Prepared by a method similar as described for 600a/103 (Step A), except 2-fluoro-4,6-dimethyl-nitrobenzene was used instead of 2-fluoronitrobenzene to give the desired 15 compound in 93% yield.

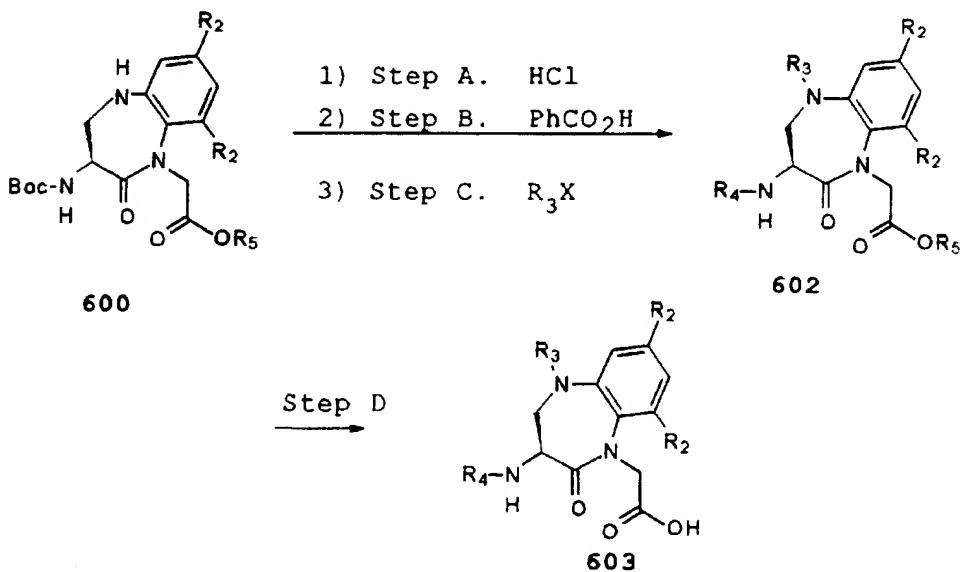
20 Step B. (2S)-2-tert-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid. (2S)-2-tert-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenyl-amino)propionic acid was converted to the title compound in quantitative yield as described in the preparation of 600a/103 (Step B).

25 Step C. 2-Oxo-(3S)-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine. A 0 °C solution of (2S)-2-tert-butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid (763 mg, 2.36 mmol) and N-methylmorpholine (483 mg, 4.78 mmol) in 60 ml of anhydrous THF was treated dropwise with isobutylchloroformate (352 mg, 2.5 mmol). The reaction was stirred for 2 h at 0 °C, at RT for 1h and purified 30 over EtOAc. The mixture was washed with aq. 5% NaHSO₄,

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sat. aq. NaHCO₃, and sat. aq. NaCl, dried over NaSO₄, and concentrated *in vacuo*. Chromatography (flash, SiO₂, 10% to 25% to 50% EtOAc/CH₂Cl₂) gave 490 mg (68%) of the desired product.

- 5 **Step D.** (3*S*)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (**600c**). (2*S*)-2-tert-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenylamino)-propionic acid was converted to **600c**, 75% by a
 10 similar method for the preparation of **600b**.



(3*S*)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (**602a**).

- Step A.** Anhydrous HCl was bubbled into a solution of
 15 (3*S*)-2-oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (**600a/103**, 4.0 g, 11.4 mmol) in 20 ml of CH₂Cl₂ for 20 min then stirred for 1 h at RT. The reaction

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was evaporated to give (3S)-2-oxo-3-amino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester hydrochloride as a white solid.

Step B. The white solid was dissolved in 70 ml of DMF
5 and benzoic acid (1.5 g, 12.3 mmol) was added. The reaction was cooled in a ice/H₂O bath and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.4 g, 12.5 mmol), 1-hydroxybenzotriazole (1.7 g, 12.6 mmol) and
10 diisopropylethylamine (3.0g, 23.2 mmol). The reaction was stirred for 18 h at RT under nitrogen atmosphere and poured onto H₂O. The aq. mixture was extracted with EtOAc (2x). The combined organic layers were washed with aq. 0.5 N NaHSO₄, H₂O, sat. aq. NaHCO₃, H₂O
15 and sat. aq. NaCl, dried over MgSO₄ and concentrated in vacuo. Chromatography (flash, SiO₂, 10% to 30% EtOAc/CH₂Cl₂) gave 3.4 g (85%) of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester as a white
20 solid.

Step C. Method A. (3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602a). A solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (200 mg, 0.57 mmol) in CH₂Cl₂(10 ml) was treated with triethylamine (119 mg, 1.13 mmol) and 3-phenylpropionyl chloride (114 mg, 0.68 mmol). The reaction was stirred at RT for 30 min and diluted with
25 CH₂Cl₂. The solution was washed with aq. 10% HCl, sat. aq. NaHCO₃ and sat. aq. NaCl, dried over Na₂SO₄ and
30

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concentrated *in vacuo* to give 240 mg (87%) of **602a** as a white foam.

Step C. Method B. (3S)-2-Oxo-3-benzoylamino-5-acetoacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-

- 5 **acetic acid benzyl ester (602g).** A 0 °C solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (**600b**) (465 mg, 1.10 mmol) in CH₂Cl₂ (5 ml) was treated with acetoacetic acid in 1 ml of CH₂Cl₂ followed by slow
- 10 addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (431 mg, 2.2 mmol) in 2 ml of CH₂Cl₂ under N₂ atmosphere. After 15 min the reaction was poured onto EtOAc, washed with aq. 5 % NaHSO₄, dried over Na₂SO₄ and concentrated *in vacuo*.
- 15 Chromatography (flash, SiO₂, 0% to 10% to 25% MeOH/CH₂Cl₂) gave 580 mg of (3S)-2-oxo-3-(benzoylamino)-5-acetoacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester as a white solid.
- 20 **Step C. Method C. (3S)-2-Oxo-3-benzoylamino-5-methoxycarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (602j).** A vigorously-stirred, 0 °C solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-
- 5 benzodiazepine-1-acetic acid benzyl ester (**600b**) (461 mg, 1.07 mmol) in THF (5 ml) and sat. aq. NaHCO₃ (2.5 ml) was treated with a THF solution (0.35 ml) of methyl chloroformate (151 mg, 1.6 mmol) and the reaction was stirred for 45 min at RT. The reaction
- 30 was poured onto CH₂Cl₂ and washed with H₂O, dried over Na₂SO₄ and concentrated *in vacuo*. Chromatography

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(flash, SiO₂, 0% to 10% MeOH/CH₂Cl₂) gave 525 mg of 602j as a white solid.

Step C. Method D. (3S)-2-Oxo-3-benzoylamino-5-
benzylaminocarbonyl-2,3,4,5-tetrahydro-1H-1,5-

5 **benzodiazepine-1-acetic acid methyl ester (602p)**. A solution of 600a/103 (400 mg, 1.1mmol) and benzylisocyanate (166 mg, 1.2mmol) in 10 ml of CH₂Cl₂ and 10 ml of DMF and heated at 80 °C for 3 days. The reaction was cooled to RT poured onto H₂O and extracted 10 with EtOAc (2x). The combined organic layers were washed with H₂O (4x) and sat. aq. NaCl, dried over MgSO₄ and concentrated *in vacuo*. Chromatography (flash, SiO₂, 50% to 80% EtOAc/hexane) gave 440 mg (80%) of 602p as a white solid.

15 **Step C. Method E. (3S)-2-Oxo-3-benzylamino-5-(3-**
phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-
benzodiazepine-1-acetic acid methyl ester (602v). A solution of (3S)-2-oxo-3-amino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid 20 methyl ester hydrochloride (560 mg, 1.34 mmol), benzaldehyde (146 mg, 1.34 mmol) and sodium acetate (220 mg, 2.68 mmol) in methanol (20 ml) was treated with 4Å sieves (2 g) and NaCNBH₃ (168 mg, 2.68 mmol). The reaction was stirred for 2.5 h, acidified with 10% aq. HCl to pH 2 and washed with Et₂O (2×75 ml). The organic layers were concentrated *in vacuo* to give an oil. Chromatography (flash, SiO₂, 0 to 35% EtOAc/CH₂Cl₂) gave 250 mg (40%) of 602v as a clear oil.

Step D. Method A. (3S)-2-Oxo-3-benzoylamino-5-(3-

30 **phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-**

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- benzodiazepine-1-acetic acid (603a).** (3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzo diazepine-1-acetic acid methyl ester (**602a**; 1.25 g, 2.57 mmol) was dissolved in 11 ml of 5 THF, MeOH and H₂O (5:5:1) and treated with LiOH•H₂O (42 mg, 0.62 mmol) stirred at RT for 64 h. The reaction was concentrated *in vacuo*, diluted with H₂O and acidified with aq. 1N HCl to give 230 mg of **603a** as a white solid.
- 10 **Step D. Method B.** (3S) 2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (**603d**). A mixture of (3S)-2-oxo-3-(benzoylamino)-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (**602d**; 510 mg, 1.08 mmol) and 15 5% Pd/C (250 mg) in MeOH (10 ml) stirred under H₂ (1 atm) for 0.5h. The reaction was filtered and concentrated *in vacuo* 410 mg of **603d** as a white solid.

The compounds of Table 8 were prepared as described in Table 9, using the methods of Example 12.

20 **Table 8**

Compound no.	R ₂	R ₃	R ₄	R ₅
602b	H	PhCH ₂ C(O)	PhC(O)	CH ₂ Ph
602c	H	PhC(O)	PhC(O)	CH ₂ Ph
25 602d	H	CH ₃ C(O)	PhC(O)	CH ₂ Ph
602e	H	CH ₃ OCH ₂ C(O)	PhC(O)	CH ₂ Ph
602f	H	(CH ₃) ₂ CHCH ₂ C(O)	PhC(O)	CH ₂ Ph
602g	H	CH ₃ C(O)CH ₂ C(O)	PhC(O)	CH ₂ Ph

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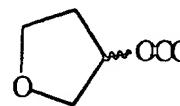
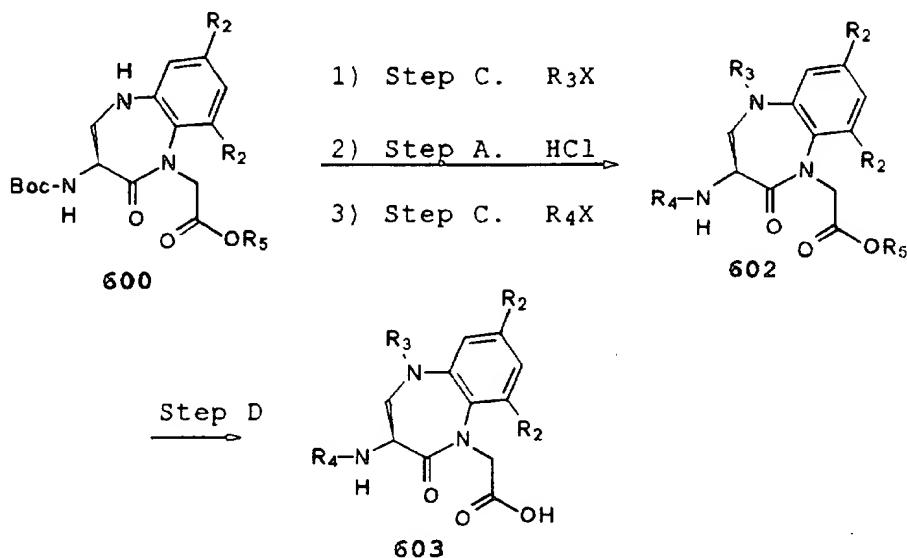
Compound no.	R ₂	R ₃	R ₄	R ₅
602h	H	CH ₃ OC(O)C(O)	PhC(O)	CH ₂ Ph
602i	H	CH ₃ C(O)C(O)	PhC(O)	CH ₂ Ph
602j	H	CH ₃ OC(O)	PhC(O)	CH ₂ Ph
602k	H	CH ₃ C(O)	Boc	CH ₂ Ph
5 602l	CH ₃	CH ₃ C(O)	Boc	CH ₂ Ph
602m	H	CH ₃ S(O ₂)	PhC(O)	CH ₃
602p	H	PhCH ₂ NHC(O)	PhC(O)	CH ₃
602q	H		PhC(O)	CH ₂ Ph
602r	H	PhCH ₂ CH ₂ C(O)	PhCH ₂ CH ₂ C(O)	CH ₂ Ph
10 602s	H	4-pyridylCH ₂ C(O)	PhC(O)	CH ₂ Ph

Table 9

No.	Starting material	R ₃ X	Step C method/ (% yield)	Step D method/ (% yield)
603b	600b	PhCH ₂ C(O)Cl	A (98)	B (89)
603c	600b	PhC(O)Cl	A (quant.)	B (quant.)
15 603d	600b	CH ₃ C(O)Cl	A (quant.)	B (quant.)
603e	600b	CH ₃ OCH ₂ C(O)Cl	A (59)	B (quant.)
603f	600b	(CH ₃) ₂ CHCH ₂ C(O)Cl	A (88)	B (95)
603g	600b	CH ₃ C(O)CH ₂ CO ₂ H	B (quant.)	B (quant.)
603h	600b	CH ₃ OC(O)C(O)Cl	A (96)	B (quant.)
20 603i	600b	CH ₃ C(O)CO ₂ H	B (87)	B (94)
603j	600b	CH ₃ OC(O)Cl	C (quant.)	B (quant.)

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No.	Starting material	R ₃ X	Step C method/ (% yield)	Step D method/ (% yield)
603k	600b	CH ₃ C(O)Cl	A, Step C only (quant.)	not run
603l	600c	CH ₃ C(O)Cl	A, Step C only (quant.)	not run
603m	600a/103	CH ₃ SO ₃ Cl, NEt ₃ instead of pyridine and THF instead of CH ₂ Cl ₂	A (76)	A (92)
603p	600a/103	PhCH ₂ C=N=O	D (80)	A (86)
5	603q	600b	C (83)	B (71)
	603r	600a/103	A	
	603s	600b	B (90)	B (98)



The compounds of Table 10 were prepared as described in Table 11 using the methods of Example 12.

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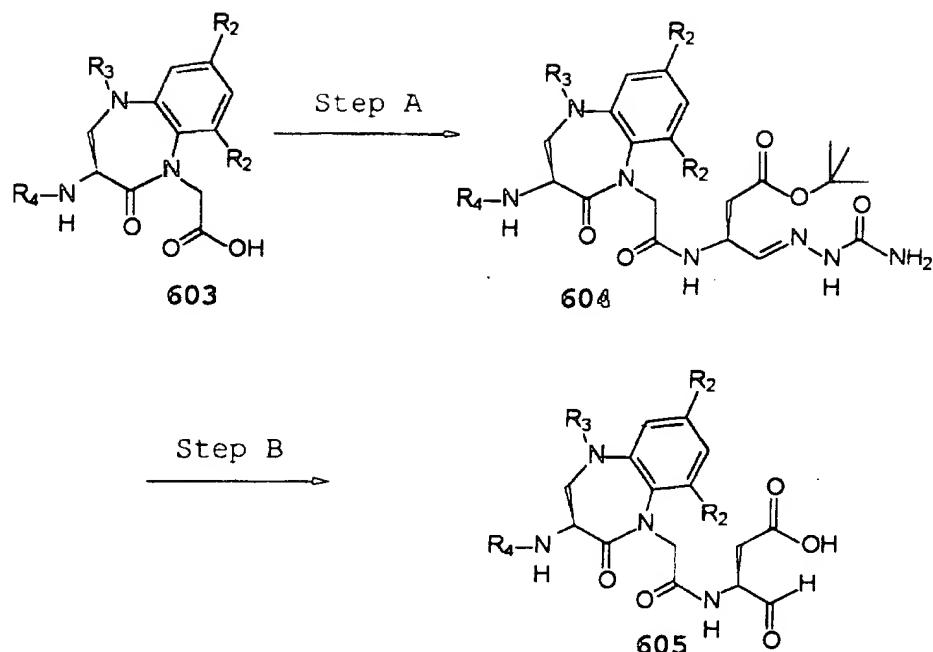
Table 10

Compound no.	R ₂	R ₃	R ₄	R ₅
5	602n	H	CH ₃ C(O)	Naphthylene-2-C(O)
	602o	CH ₃	CH ₃ C(O)	PhC(O)
	602t	H	3-CH ₃ PhCH ₂ C(O)	PhC(O)
	602u	H	CH ₃ C(O)	Fmoc
	602v	H	PhCH ₂ CH ₂ CO	PhCH ₂

Table 11

No.	Starting material	1) Step C. R ₃ X method (% yield)	3) Step C R ₄ X method (% yield)	Step D method (% yield)
10	603n	602k	CH ₃ C(O)Cl A (quant.)	naphthylene- 2-C(O)Cl A (70)
	603o	602l	CH ₃ C(O)Cl A (quant.)	PhC(O)Cl A (73)
	603t	602k	3- CH ₃ PhCH ₂ C(O)Cl A (quant.)	PhC(O)Cl A (93)
15	603u	602k	CH ₃ C(O)Cl A (quant.)	Fmoc-Cl C (82)
	603v	600a/103	PhCH ₂ CH ₂ C(O)Cl A	PhCHO E (40)

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The compounds of Table 12 were prepared by the methods described below.

Table 12

	compound no.	R₂	R₃	R₄
5	605a	H	PhCH ₂ CH ₂ C(O)	PhC(O)
	605b	H	PhCH ₂ C(O)	PhC(O)
	605c	H	PhC(O)	PhC(O)
	605d	H	CH ₃ C(O)	PhC(O)
	605e	H	CH ₃ OCH ₂ C(O)	PhC(O)
	605f	H	(CH ₃) ₂ CHCH ₂ C(O)	PhC(O)
	605g	H	CH ₃ C(O)CH ₂ C(O)	PhC(O)
	605h	H	CH ₃ OC(O)C(O)	PhC(O)
	605i	H	CH ₃ C(O)C(O)	PhC(O)
	605j	H	CH ₃ OC(O)	PhC(O)

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compound no.	R ₂	R ₃	R ₄
605m	H	CH ₃ SO ₃	PhC(O)
605n	H	CH ₃ C(O)	Naphthyl-2-C(O)
605o	CH ₃	CH ₃ C(O)	PhC(O)
605p	H	PhCH ₂ NHC(O)	PhC(O)
5 605q	H		PhC(O)
605s	H	4-pyridylCH ₂ C(O)	PhC(O)
605t	H	3-CH ₃ PhCH ₂ C(O)	PhC(O)
605v	H	PhCH ₂ CH ₂ C(O)	PhCH ₂

(3S)-3-[(3S) -2-Oxo-3-benzoylamino-5-(3-
10 phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-
benzodiazepin-1-acetylamino]4-oxo-butyric acid (605a).

Step A. (3S)-3-(1-Fluorenylmethyloxycarbonylamino)-4-oxobutyric acid tert-butyl ester semicarbazone (210 mg, 0.45 mol, Prepared in a similar manner to the
15 benzyloxycarbonyl analog in Graybill et al., Int. J. Protein Res., 44, pp. 173-82 (1994).) was dissolved in 10 ml of DMF and 2 ml of diethylamine and stirred for 2 h. The reaction was concentrated *in vacuo* to give (3S)-3-amino-4-oxobutyric acid tert-butyl ester
20 semicarbazone. The 0 °C solution of the above residue and 603a (200 mg, 0.42mmol) in 5 ml of DMF and 5 ml of CH₂Cl₂ was treated with 1-hydroxybenzotriazole (57 mg, 0.42mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (98 mg, 0.51 mmol).
25 The reaction was stirred at RT for 18 h, poured onto

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EtOAc (75 ml) and washed with aq. 0.3 N KHSO₄, sat. aq. NaHCO₃ and sat. aq. NaCl, dried over NaSO₄ and concentrated *in vacuo*. Chromatography (flash, SiO₂, 0% to 4% MeOH/0.1% NH₄OH/CH₂Cl₂) to give 240 mg (83%) of

5 **604a.**

Step B. **604a** was stirred with 10 ml of 33% TFA/H₂O for 4 h and concentrated *in vacuo*. The residue was dissolved in 7 ml of MeOH/acetic acid/37% aq. formaldehyde (5:1:1) and stirred for 18 h.

10 Chromatography (Reverse Phase C18, 4.4mm ID x 25 cm, 15% to 70% CH₃CN/0.1% TFA/H₂O) gave 32 mg (16%) of **605a** as a white solid: ¹H NMR (CD₃OD, existing as diastereomers of the hemiacetal) δ 7.85-7.78 (2H, d), 7.5-7.32 (6H, m), 7.32-7.28 (1H, m), 7.18-6.98 (5H, m), 15 4.92-4.85 (2H, m), 4.5-4.32 (2H, m), 4.31-4.20 (2H, m), 3.7-3.6 (1H, m), 2.90-2.75 (2H, m), 2.65-2.5 (1H, m), 2.48-2.25 (3H, m).

The following compounds were prepared by a similar method:

20 **(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-phenylacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605b)**. 148 mg (33%) as a white solid: ¹H NMR(CD₃OD) δ 7.9-6.9 (m, 16H), 4.9 (s, 2H), 4.5 (m, 1H), 4.4 (m, 2H), 3.75 (s, 1H), 3.6 (dd, 1H), 3.45 (dd, 1H), 2.7 (m, 1H), 2.5 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-benzoyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605c). 319 mg (56%) as a white solid: ¹H NMR(CD₃OD) δ 7.9-6.9 (m, 16H), 5.1 (m, 1H), 4.9 (dd,

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1H), 4.7 (m, 1H), 4.6 (dd, 1H), 4.4 (m, 2H), 4.05 (m, 1H), 2.7 (m, 1H), 2.5 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-

5 butyric acid (605d). 190 mg (38%) as a white solid:

¹H NMR (CD₃OD) δ 1.9 (d, H), 2.4 (m, 1H), 2.65 (m, 1H), 3.7 (m, 1H), 4.25 (m, 1H), 4.45 (m, 2H), 4.8-5.05 (m, 3H), 7.3-7.7 (m, 7H), 7.9 (d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methoxyacetyl-

10 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605e). 250 mg (78%)
¹H NMR (CD₃OD) δ 1.87 (bs), 1.95 (s, 2H), 2.1 (bs), 2.4 (m, 2H), 2.65 (m, 2H), 3.59 (bs), 3.75 (bs), 3.87 (bs), 4.19 (m), 4.37 (m), 4.50-4.78 (bm), 4.92 (m), 5.27 (bs), 7.41-7.58 (m, 7H), and 7.87 ppm (d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-methylbutyryl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

acetylamino]4-oxo-butyric acid (605f). 210.5 mg (46%)

as a white solid: ¹H NMR (CD₃OD) δ 7.9-7.4 (m, 9H), 5.1 (m, 1H), 4.9 (m, 1H), 4.6 (dd, 1H), 4.4 (m, 2H), 4.1 (d, 1H), 3.8 (m, 1H), 3.5 (q, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.0 (m, 3H), 1.2 (t, 1H), 0.9 (d, 3H), 0.8 (d, 3H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetoacetyl-

25 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605g). 81 mg (19%) as
a white solid: ¹H NMR (CD₃OD) δ 7.9-7.3 (m, 11H), 4.9-4.8 (m, 2H), 4.6-4.4 (m, 3H), 4.3 (m, 1H), 3.75 (q,

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1H), 3.55 (d, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.05 (s, 3H).

**(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methyloxalyl-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-**

5 **acetylamino]4-oxo-butyric acid (605h)**. 227 mg (54%) of a white solid: ^1H NMR(CD₃OD) δ 2.5(m, 1H), 2.7(m, 1H), 3.55(s, 3H), 3.8-4.0(m, 2H), 4.4(m, 1H), 4.6-4.8(m, 2H), 4.95(d, 1H), 5.1(m, 1H), 7.3-7.7(m, 7H), 7.9(d, 2H), 8.6(d, 1H).

10 **(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetylcarbonyl-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-**
acetylamino]4-oxo-butyric acid (605i). 150 mg (37%) as a white solid: ^1H NMR(CD₃OD) δ 7.9-7.3 (m, 12H), 5.1 (m, 1H), 4.65 (t, 1H), 4.55 (dd, 1H), 4.35 (m, 1H), 4.1 15 (d, 1H), 3.9 (q, 1H), 3.45 (q, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.25 (s, 3H).

**(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methoxycarbonyl-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-**
acetylamino]4-oxo-butyric acid (605j). 234 mg (44%) as 20 a white solid: ^1H NMR(CD₃OD) δ 7.9-7.4 (m, 12H), 5.0 (m, 1H), 4.8-4.5 (m, 3H), 4.4 (m, 1H), 4.3 (t, 1H), 3.9-3.75 (m, 2H), 3.6 (s, 3H), 2.7 (m, 1H), 2.5 (m, 1H).

**(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methanesulfonyl-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-**
acetylamino]4-oxo-butyric acid (605m). 64.5 mg (34%) as a white solid: ^1H NMR (DMSO-d₆, existing as diastereomers of the hemiacetal & open form of the aldehyde) δ 9.48 (0.2H, s), 8.85-8.72 (1H, m), 8.65-

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8.60 (0.8 H, d), 8.30-8.26 (0.2 H, d), 7.95-7.88
(2H, d), 7.6-7.45 (6H, m), 7.44-7.38 (1H, m), 5.78-5.75
(0.2H, d), 5.48 (0.6H, s), 4.85-4.70 (2H, m), 4.62-4.54
(1H, d), 4.50-4.40 (2H, m), 4.25-4.14 (1H, m), 3.9-3.85
5 (1H, m), 3.16 (3H, s), 3.05-2.3 (2, m).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(naphthlene-2-carbonyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605n). 103 mg (17%) as
a white solid: ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.5(m,
10 1H), 2.65(m, 1H), 3.75(m, 1H), 4.3(m, 1H), 4.5-4.7(m,
3H), 4.85-5.1(m, 2H), 7.3-7.65(m, 6H), 7.85-8.05(m,
4H), 8.45(s, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605o). 42 mg (12%) as
15 a white solid: ^1H NMR (CD_3OD , existing as
diastereomers of the hemiacetal) δ 7.85-7.74 (2H, m),
7.5-7.44 (1H, m), 7.43-7.35 (4H, m), 5.6-5.05 (2H, m),
4.82-4.42 (2H, m), 4.40-3.95 (2H, m), 3.6-3.5 (1H, m),
20 2.7-2.38 (2H, m), 2.32 (3H, s), 2.27 (3H, s), 1.92
(3H, s).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-benzylaminocarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605p). 165
25 mg (37%) as a white solid: ^1H NMR (CD_3OD) δ 2.45(m,
1H), 2.7(m, 1H), 3.8(m, 1H), 4.15-4.5(m, 4H), 4.5-
4.75(m, 2H), 4.8-5.0(m, 2H), 7.1-7.7(m, 12H), 7.9(d,
2H).

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(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-[(3R,S) 3-tetrahydrofurylmethyoxy carbonyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetyl amino]4-oxo-butyric acid

(605q). 210 mg (66%) ^1H NMR (CD_3OD) δ 1.95 (s, 2H),

5 2.4 (m, 2H), 2.65 (m, 2H), 3.29 (s, 3H), 3.78 (m), 3.87 (bs), 4.0 (d, 1H), 4.32 (m), 4.50-4.15 (m), 4.95 (m), 5.27 (bs), 7.45-7.65 (m, 7H), and 7.89 ppm (d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(4-pyridylacetyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

10 acetyl amino]4-oxo-butyric acid (605s). 128 mg (19%) as a white solid: ^1H NMR (CD_3OD) δ 8.5-7.4 (m, 13H), 5.0 (m, 1H), 4.7 (m, 1H), 4.5 (m, 2H), 4.45-4.4 (m, 3H), 3.8-3.7 (m, 2H), 2.7 (m, 1H), 2.5 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-

15 methylphenylacetyl)-2,3,4,5-tetrahydro-1H-1,5-

benzodiazepin-1-acetyl amino]4-oxo-butyric acid (605t).

132 mg (24%) as a white solid: ^1H NMR (CD_3OD) δ 7.8-6.7 (m, 13H), 4.9 (t, 1H), 4.75 (dd, 1H), 4.2 (dd, 1H), 4.1 (m, 2H), 3.8 (dd, 1H), 3.6 (q, 1H), 3.45 (dd, 1H), 3.3

20 (dd, 1H), 2.6 (m, 1H), 2.3 (m, 1H), 2.15 (s, 3H).

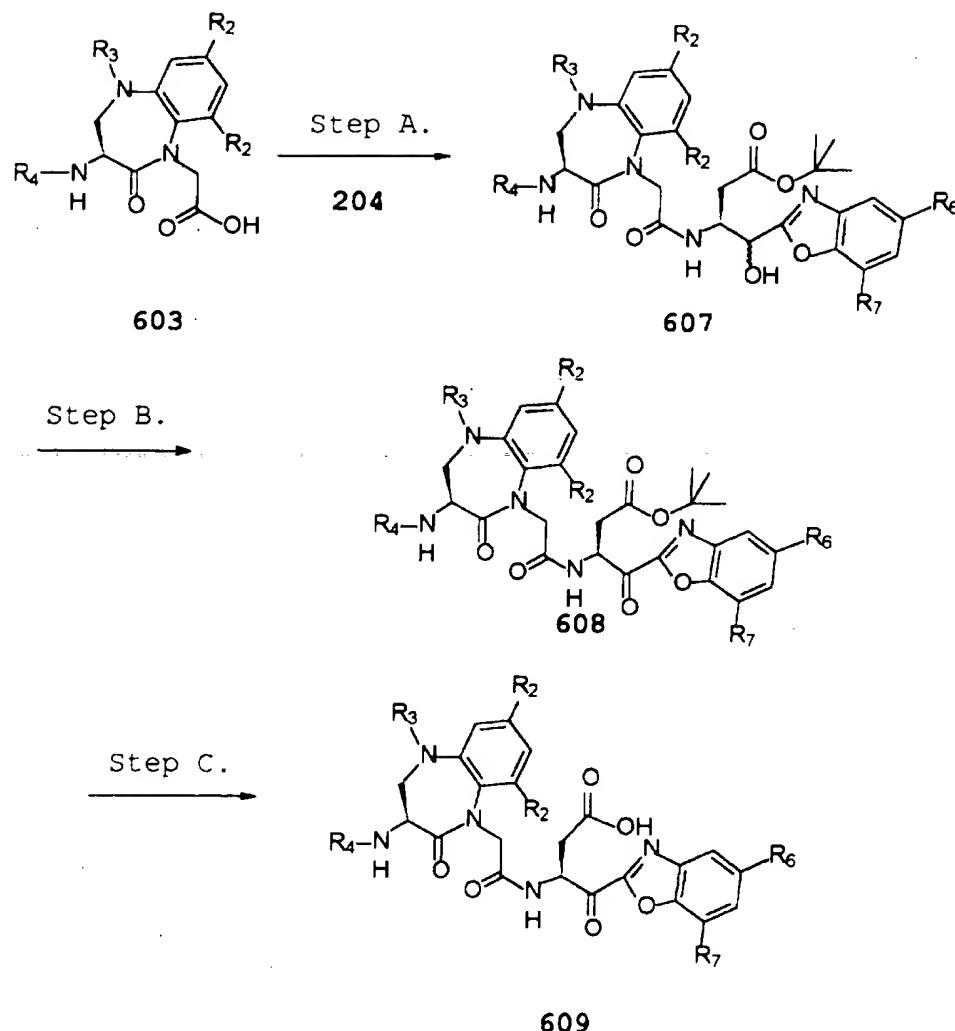
(3S)-3-[(3S)-2-Oxo-3-benzylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

acetyl amino]4-oxo-butyric acid trifluoroacetic acid

salt (605v). 88 mg (28%) as a white solid: ^1H NMR

25 (CD_3OD) δ 7.63-7.51 (2H, m), 7.5-7.35 (7H, m), 7.25-7.10 (3H, m), 7.1-7.02 (2H, m), 5.04-4.96 (1H, m), 4.75-4.57 (2H, m), 4.38-4.35 (2H, m), 4.24-4.12 (2H, m), 4.10-4.02 (1H, d), 4.88-4.75 (1H, m), 2.90-2.80 (2H, m), 2.78-2.63 (1H, m), 2.55-2.35 (2H, m), 2.34-2.22 (1H, m).

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The compounds of Table 13 are described below.

Table 13

#	R ₂	R ₃	R ₄	R ₆	R ₇
609a	H	PhCH ₂ CH ₂ C(O)	PhCH ₂ CH ₂ C(O)	Cl	Cl
609b	H	CH ₃ C(O)	PhC(O)	Cl	Cl

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(3S)-3-[(3S)-2-Oxo-3-(3-phenylpropionylamino)-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609a).

5 Step A. A solution of 204 (223 mg, 0.5 mmol) and 603r (300mg; 0.36 mmol) in 4 ml of DMF and 4 ml of CH₂Cl₂ was treated with (Ph₃P)₂PdCl₂ (10 mg), 1-hydroxybenzotriazole (135 mg, 1.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (115 mg, 0.6 mmol). Tri-n-butyl tin hydride (219 mg, 0.75 mmol) was added dropwise to the reaction and stirred for 18 h. The reaction was poured onto EtOAc and washed with aq. 10% NaHSO₄, sat. aq. NaHCO₃ and sat. aq. NaCl, dried over Na₂SO₄ and concentrated *in vacuo*. Chromatography (flash, SiO₂, 0% to 50% EtOAc/hexane) gave 360 mg (86%) of 607a as a foam.

10 Step B. A solution of 607a (360 mg) in 5 ml of CH₂Cl₂ was added dropwise to a suspension of 1,1,1-triacetoxy-1,1-dihydro-1,2-benzioldioxol-3(1H)-one (362 mg, 0.85 mmol) in 20 ml of CH₂Cl₂. The reaction was stirred for 4.5 h, diluted with CH₂Cl₂ and washed with a 1:1 mixture of sat. aq. NaHCO₃/sat. aq. Na₂S₂O₃, sat. aq. NaHCO₃ (2x) and sat. aq. NaCl, dried over Na₂SO₄ and concentrated *in vacuo*. Chromatography (flash, SiO₂, 20% EtOAc/CH₂Cl₂) gave 340 mg (95%) of the ketone 608a.

15 Step C. 608a (300 mg, 0.36 mmol) was dissolved in 25 ml of 25% TFA/CH₂Cl₂ and stirred at RT for 5 h and concentrated *in vacuo*. Chromatography (flash, SiO₂, 0 to 5% MeOH/CH₂Cl₂) gave 118 mg (42%) of 609a as a white solid: ¹H NMR (CD₃OD) δ 7.62-6.65 (16H, m), 4.85-4.7